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The Medical Bulletin of Haseki is the official scientific journal of the University of Health Sciences Haseki Training and Research Hospital. It covers subjects on general medicine, published both in Turkish and English, and is independent, peer-reviewed, international periodical and is published quarterly (March, June, September and December).

The aim of The Medical Bulletin of Haseki is to publish original research papers of highest scientific and clinic value on general medicine. Additionally, educational material reviews on basic developments, editorial short notes and case reports are published.

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The Medical Bulletin of Haseki

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The manuscript should not exceed 5000 words in total. All pages of the manuscript should be numbered at the top right-hand corner, except for the title page. Papers should include the necessary number of tables and figures in order to provide better understanding.

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Case Report

Original Article

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Hyaluronic Acid Gel as an Outer Ear Canal Packing Following Tympanoplasty: A Randomized Controlled Study

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Abstract

Aim: In search of better alternative material than gelatin sponge dressing (GSD) traditionally used in the external ear canal after tympanoplasty, it's aimed to evaluate the use of new cross-linked hyaluronic acid gel (HYA) and compare it with GSD.

Methods: This block-randomized controlled trial was performed in 50 patients who underwent tympanoplasty between April and December 2019. The patients were divided into two groups according to external ear filling material (HYA as study group n=25, GSD as control group n=25). The groups were compared in terms of edema, pain, graft morphology, epithelization, drainage parameters at postoperative 1st, 2nd, 3rd, and 4th weeks. In addition, pure-tone audiometry and graft success were also evaluated.

Results: After the first week, edema in HYA was significantly less than GSD (p=0.033). Reaching the 2nd week, less discharge was observed in HYA (p=0.007). Third week results showed edema in HYA was significantly less than that of GSD (p=0.023). In the 4th week, the postoperative gap gain in the HYA group was significantly higher than GSD (p=0.037). The difference in graft intake between groups was not significant (p=0.189).

Conclusion: New cross-linked HYA gel may act as a promoter in the healing process after tympanoplasty and may have positive effects on hearing restoration.

Keywords: Hyaluronic acid, gelatin, tympanoplasty, ear canal

Introduction

Tympanic membrane perforation is one of the main causes of conductive hearing loss (1). Perforations often heal spontaneously to a greater extent requiring no further surgical intervention. Surgical repair of the tympanic membrane is a safe and proven method in susceptible cases. The success of the operation depends on the integrity of the tympanic membrane graft, maintaining adequate ventilation of the tympanum and dry ear with improved or at least preserved hearing function. Beyond high success rates, that operation possesses some complications such as graft medialization or lateralization, epithelialization problems in the external ear canal (EEC), stenosis, iatrogenic cholesteatoma; some of which may require further attention (2). To achieve good wound healing and graft integrity are the essentials to minimize complications. Therefore, absorbable and non-absorbable packing materials are used to support the graft and EEC and to prevent adhesions (3). Besides certain advantages, EEC packing reduces the quality of life and may provoke hypersensitivity reactions (4).

Hyaluronic acid (HYA) is a natural component of the extracellular matrix of body tissues. It stimulates the release of endogenous growth factors, epidermal growth factors, insulin growth factor, tumor necrosis factor and vascular endothelial growth factor (5). There are studies involving its use in myringoplasty (6), adhesive otitis media and mastoidectomy operations in otology (7,8). Currently, several HYA products with different formulations are used

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in otology (9). Recently, we acquired a new cross-linked HYA gel and began to use it in our clinical expertise; this product has a self cross-linked technology between HYA molecules. It is thought to have a controlled bio-absorption profile and the viscosity of the HYA is adapted to the critical tissue repair process. HYA leaves no potential space providing ease of application to the desired area. We, therefore, aimed to investigate the effects of this new molecule on EEC and graft after tympanoplasty operations.

Methods

Study Design

This study was approved by the ethics committee of Marmara University Faculty of Medicine (09.2019.199) and carried out in Prof. Dr. Cemil Tascioglu City Hospital. This randomized controlled study was performed on 50 ears of 50 patients between April and December 2019; cases were randomly and equally assigned either to HYA (PureRegen® Gel OTOL, BioRegen Biomedical Co. Ltd., Changzhou, China) or to gelatin sponge dressing group (GSD; Spongostan, Ethicon, New Jersey, USA). The GSD group was assigned as a control group and block randomization method was used for randomization. Informed consent was obtained from all patients. Inclusion criteria were chronic tympanic membrane perforation, age below sixty years, air-bone gap below 30 dB in pure tone audiometry and dry ear for at least the last 3 months. Exclusion criteria were previous ear surgery, smoking, diabetes, hypertension, ischemic heart disease, rheumatological disease or sinonasal pathology of any kind. The flow diagram of the study according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 is presented in Figure 1.

Operation Technique

All surgeries were performed by the senior author (D.H.). All patients were operated under the condition of general anaesthesia through a retroauricular approach. A tragal island graft was prepared with a notch suitable for malleus insertion. After the underlay insertion of the harvested graft, the tympanic membrane and the outer ear was either filled with HYA or GSD randomly. A regimen of antibiotic therapy (ciprofloxacine 750 mg BID) and non-steroidal anti-inflammatory drug (NSAID) treatment (etodolac 400 mg BID), was applied for one week as a postoperative routine in our clinic. EEC dressing was opened on the 7th day.

Postoperative Follow-up

The postoperative monitoring and controls were assessed by a different surgeon (B.G.). Weekly controls were made for one month postoperatively. Edema was scored as low in cases of swelling between 0%-25% of EEC, moderate in 25%-75%, and high in more than 75%. Pain is scored as Yes=pain requiring NSAIDs or No=pain not requiring NSAIDs. EEC epithelialization was classified as complete epithelialization, partial granulation or advanced granulation. Morphology of the graft was classified as pale, partially vascularized or completely vascularized. EEC discharge was noted and classified as discharge requiring topical antibiotics or discharge requiring topical and systemic antibiotics. On the postoperative 4th week, a repeat pure tone audiometry was performed for each patient.

Statistical Analysis

Statistical analyses were performed using the SPSS software version 23 (IBM, Turkey). The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine the normal distribution. Descriptive analyses were presented as mean, standard deviations, median, minimum and maximum. Chi-square test or Fisher's Exact test was used to compare proportions in different groups. Mann-Whitney U test and Student's t-tests were used to compare means in different groups. P-value less than 0.05 was accepted as statistically significant.

Results

Scores of the postoperative first week (Table 1) showed no significant difference between groups in terms of pain (p=0.758) and discharge (p=1.000). The graft morphology could not be evaluated microscopically due to EEC edema. The epithelization in HYA was faster than GSD (p=0.077). The edema in HYA was significantly less than GSD (p=0.033). In the second week, both groups had less edema, pain, discharge and better epithelization compared to the first postoperative week. There was no significance among the two groups in terms of edema (p=0.258), pain (p=0.758) and graft morphology (p=0.615). Epithelization in HYA was faster than GSD, but the scores were not statistically significant (p=0.070). Complete epithelization was observed in 40% (n=10) in HYA whereas 16% (n=4) in GSD. Significant less discharge was observed in HYA (p=0.007). The third week revealed less edema, pain, discharge, better epithelization and better graft morphology compared to the second postoperative week. No significance was found between the two groups in terms of pain (p=0.508), discharge (p=0.185) and graft morphology (p=0.225). The edema in HYA was significantly less than GSD (p=0.023). 60% (n=15) HYA patients had no edema while it was 28% (n=7) in GSD. The epithelization in HYA was significantly faster than GSD (p=0.037). Complete epithelization was observed in 80% (n=20) HYA and 52% (13) GSD.

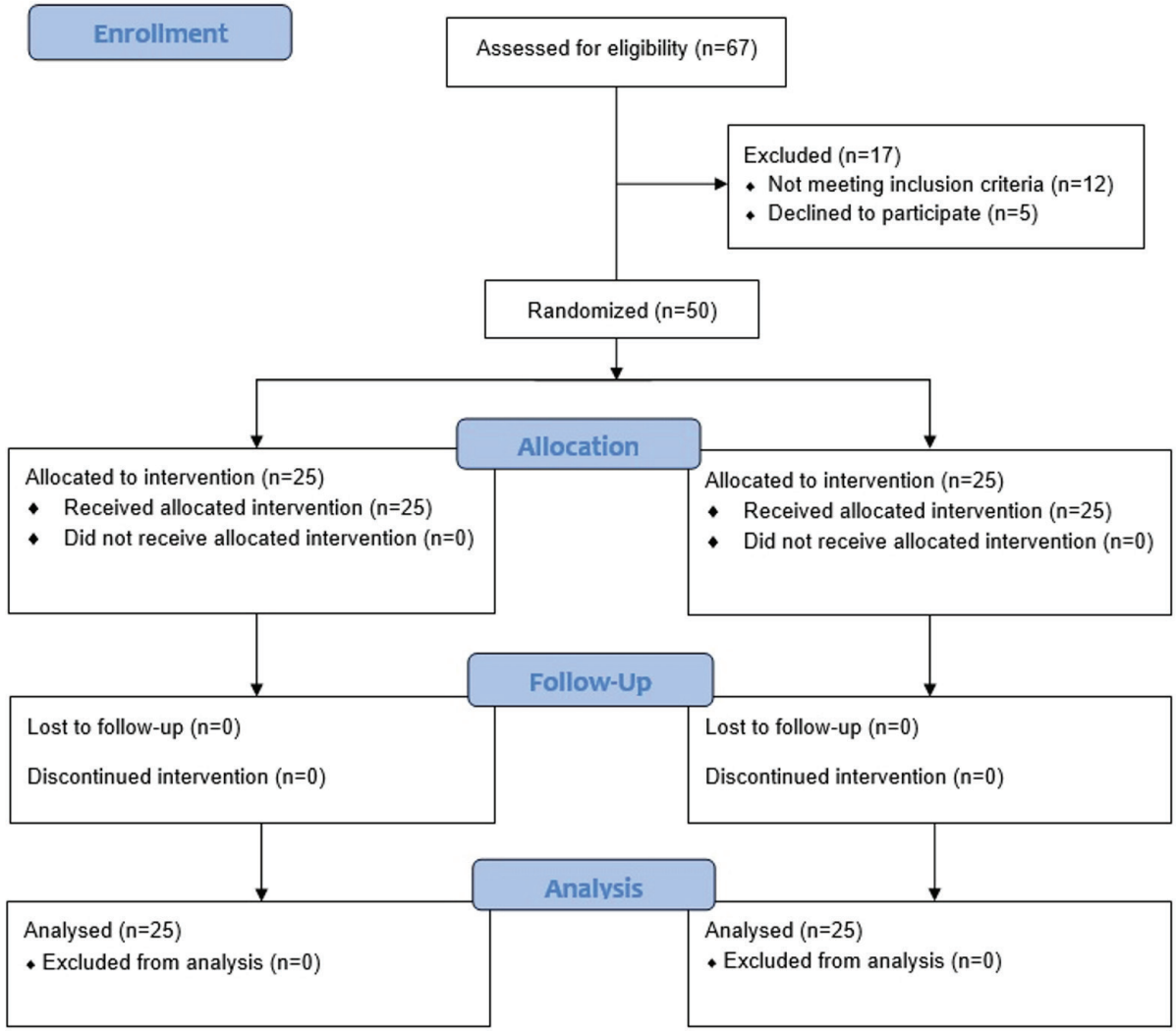

Figure 1. CONSORT 2010 flow diagram

The clinical outcomes on the postoperative fourth week showed that 100% (n=25) HYA had no edema nor pain and achieved complete epithelization of EEC while in GSD, 12% (n=3) had minimum edema, 16% (n=4) had partial granulation. Full vascularization was observed in 92% (n=23) of HYA and 84% (n=21) of GSD.

The results of preoperative and postoperative first-month audiometry tests of both groups are shown in Table 2. Preoperative air conduction (p=0.377) and bone conduction (p=0.143) was not significant between the two groups. Postoperative bone conduction was not significant between the two groups (p=0.141). The difference in the postoperative air conduction between the two groups was also not significant but close to being significant (p=0.070). The gap gain in HYA (15.2±5.2 dB) was significantly higher than GSD (11±6.1 dB) (p=0.037) (Table 2).

The success rate of graft in HYA was higher than the GSD. In HYA, the graft intake was successful in 24 patients (96%) with one failure (4%) only whereas in GSD the graft intake was successful in 20 patients (80%) with five failure (20%). Graft intake between groups was not significant (p=0.189).

Discussion

It is a routine to fill the EEC with absorbable/non-absorbable materials in order to prevent ear canal deformity or EEC stenosis at the end of ear surgery. However, the risk of displacement of the graft still remains during the insertion and removal of the packing material. Non-absorbable materials include ear-wick, silastic sheet or gauze with ointments. Absorbable materials can be in the form of gelatin sponge (Spongostan) or Tri-Adcortyl/Polyfax ointment. Absorbable materials are usually

Table 1. Postoperative comparative results

		Postoperative first week			Postoperative second week			Postoperative third week			Postoperative fourth week		
		HYA (n=25)	GSD (n=25)	p[α]	HYA (n=25)	GSD (n=25)	p[α]	HYA (n=25)	GSD (n=25)	p[α]	HYA (n=25)	GSD (n=25)	p[α]
Edema	-	-	-	**0.033***	-	-	0.258	-	-	**0.023***	-	-	0.235
	No	0 (0%)	0 (0%)	-	1 (4%)	0 (0%)	-	15 (60%)	7 (28%)	-	25 (100%)	22 (88%)	-
	Low	8 (32%)	1 (4%)	-	14 (56%)	10 (40%)	-	10 (40%)	18 (72%)	-	0 (0%)	3 (12%)	-
	Moderate	11 (44%)	13 (52%)	-	10 (40%)	15 (60%)	-	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
	High	6 (24%)	11 (44%)	-	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Pain	-	-	-	0.758	-	-	0.758	-	-	0.508	-	-	1.000
	No	0 (0%)	0 (0%)	-	6 (24%)	6 (24%)	-	20 (80%)	18 (72%)	-	25 (100%)	25 (100%)	-
	Yes (no NSAID)	17 (68%)	18 (72%)	-	1 (4%)	5 (20%)	-	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
	Yes (requiring NSAID)	8 (32%)	7 (28%)	-	18 (72%)	14 (56%)	-	5 (20%)	7 (28%)	-	0 (0%)	0 (0%)	-
Discharge	-	-	-	1.000	-	-	**0.007***	-	-	0.185	-	-	0.667
	Dry	0 (0%)	0 (0%)	-	13 (52%)	4 (16%)	-	21 (84%)	17 (68%)	-	23 (92%)	21 (84%)	-
	Topical antibiotic	18 (72%)	18 (72%)	-	12 (48%)	21 (84%)	-	4 (16%)	8 (32%)	-	2 (8%)	4 (16%)	-
	Oral + topical antibiotic	7 (28%)	7 (28%)	-	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Epithelization	-	-	-	0.077	-	-	0.070	-	-	0.037*	-	-	0.110
	Complete	0 (0%)	0 (0%)	-	10 (40%)	4 (16%)	-	20 (80%)	13 (52%)	-	25 (100%)	21 (84%)	-
	Granulation (partial)	19 (76%)	13 (52%)	-	15 (60%)	19 (76%)	-	5 (20%)	12 (48%)	-	0 (0%)	4 (16%)	-
	Granulation (advanced)	6 (24%)	12 (48%)	-	0 (0%)	2 (8%)	-	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-
Graft morphology	-	-	-	-	-	-	0.615	-	-	0.225	-	-	0.667
	Full vascularization	-	-	-	4 (16%)	4 (16%)	-	19 (76%)	15 (60%)	-	23 (92%)	21 (84%)	-
	Partial vascularization	-	-	-	17 (68%)	14 (56%)	-	6 (24%)	10 (40%)	-	2 (8%)	4 (16%)	-
	Pale	-	-	-	4 (16%)	7 (28%)	-	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	-

[α]: Chi-square test, *p<0.05. HYA: New crosslinked hyaluronic acid gel, GSD: Gelatine sponge dressing, NSAID: Non-steroidal anti-inflammatory drug

removed within the first 2-3 weeks after surgery. This is an office procedure that requires no anaesthesia. However, non-absorbable materials often cause pain on removal and may displace the graft (10). Yazama et al. (11) evaluated retrospectively the factors affecting the postoperative hearing improvement in patients who underwent type IV tympanoplasty. They claimed that the packing material placed in the outer ear canal affected the postoperative hearing results. Hearing improvement in the shredded gauze group was significantly higher than the Spongel® group. In the present study, the postoperative gap gain in the HYA group is higher than in the GSD group.

HYA is found in the extracellular matrix of human tissue and is a natural polysaccharide. The main components are beta-glucuronic acid and N-acetyl-D glucosamine. It contributes considerably to viscoelastic properties and hydration regulation for soft tissue. HYA can be used safely and easily in clinical applications (12). HYA is advisable

Table 2. Postoperative pure tone audiometry					
	HYA (n=25)		GSD (n=25)		p
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Air conduction (dB)					
Preoperative	32±5.3	34 (24-45)	34±4.5	35 (26-42)	0.377**
Postoperative	18±4.9	16 (12-28)	22±6.9	22 (12-34)	0.070**
Bone conduction (dB)					
Preoperative	13±4.0	13 (6-20)	11±3.4	12 (5-18)	0.143**
Postoperative	13±4.0	13 (8-24)	11±6.1	11 (2-24)	0.141**
Gap gain (dB)	15±5.2	13 (8-24)	11±6.1	11 (2-24)	0.037*

*: Mann-Whitney U test, **: Student's t-test, p<0.05, HYA: Hyaluronic acid gel, GSD: Gelatine sponge dressing, SD: Standard deviation, min: Minimum, max: Maximum

in otology because of its non-inflammatory property. It provides a viscoelastic environment by holding water depending on its physical properties. Thus, it is thought to play a role in facilitating the healing of the fibrous layer by preventing dehydration (13). PureRegen® Gel OTOL is a new cross-linked HYA gel with controlled degradation and optimum viscosity designed for outer and middle ear surgery.

In our study, it was observed that the edema in the HYA group was significantly less in the first week. Histologically, edema is one of the main components of the inflammatory response that adversely affects wound healing. During the edema, microcirculation failure develops due to the pressure increase in the interstitial distance, thereby reducing wound site oxygenation and tissue nutrition. Accordingly, the exudate occurring at the wound site cannot be removed, which negatively affects wound healing and also prepares the ground for infection (14).

We also observed that the discharge in HYA was significantly lower in the second week. Abundant discharge may be the result of a decrease in general tissue oxygenation and the accumulation of uncleaned exudate that occurs with edema. Additionally, excess topical ciprofloxacin may impede the regeneration of the tympanic membrane (15). On the other hand, there are data reporting that HYA prevents biofilm formation. Bacterial colonization can also be blocked with an inhibitor that interferes with ligand-receptor interaction for bacterial binding. One of these inhibitors is HYA (16).

Epithelization at the 3rd week in HYA was completed earlier in our study. Martini et al. (8) also reported that re-epithelialization and graft properties were better in HYA. Studies have shown that HYA stimulates growth factors such as endogenous growth factor, tumor necrosis factor, insulin growth factor, vascular endothelial growth factor (5). Also, it has been reported that these factors stimulate revascularization, cell growth and differentiation in the healing process of the tympanic membrane (17). HYA is frequently used in tympanic membrane perforations due to this feature. Alhabib et al. (6) compared the effectiveness of platelet-rich plasma (PRP) and HYA in patients with fat myringoplasty. Graft success was statistically significant in the HYA group. In our study, although graft success was higher in HYA, this difference was not statistically significant. We believe, if the number of patients was more, our results could be positive in favor of HYA.

Study Limitation

The most important limitation of the study is that some of the parameters examined and compared postoperatively are based on subjective evaluation. In addition, there is a need for a study with more participants.

Conclusion

An ideal EEC packing should stabilize flaps by taking the shape of EEC, do not cause infection, accelerate healing and provide patient comfort. The use of new cross-linked HYA gel for packing after ear surgery meets these expectations as well as providing patient comfort.

Authorship Contributions

Concept: D.H., S.K., O.U., B.G., Y.U., Design: D.H., S.K., O.U., B.G., Y.U., Data Collection or Processing: D.H., S.K., O.U., B.G., Y.U., Analysis or Interpretation: D.H., S.K., O.U., B.G., Y.U., Literature Search: D.H., S.K., O.U., B.G., Y.U., Writing: D.H., S.K., O.U., B.G., Y.U.,

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Discrimination of Malignant and Benign Breast Masses Using Computer-Aided Diagnosis from Dynamic Contrast-Enhanced Magnetic Resonance Imaging

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Abstract

Aim: To reduce operator dependency and achieve greater accuracy, the computer-aided diagnosis (CAD) systems are becoming a useful tool for detecting noninvasively and determining tissue characterization in medical images. We aimed to suggest a CAD system in discriminating between benign and malignant breast masses.

Methods: The dataset was composed of 105 randomly breast magnetic resonance imaging (MRI) including biopsy-proven breast lesions (53 malignant, 52 benign). The expectation-maximization (EM) algorithm was used for image segmentation. 2D-discrete wavelet transform was applied to each region of interests (ROIs). After that, intensity-based statistical and texture matrix-based features were extracted from each of the 105 ROIs. Random Forest algorithm was used for feature selection. The final set of features, by random selection base, splatted into two sets as 80% training set (84 MRI) and 20% test set (21 MRI). Three classification algorithms are such that decision tree (DT, C4.5), naive bayes (NB), and linear discriminant analysis (LDA) were used. The accuracy rates of algorithms were compared.

Results: C4.5 algorithm classified 20 patients correctly with a success rate of 95.24%. Only one patient was misclassified. The NB classified 19 patients correctly with a success rate of 90.48%. The LDA Algorithm classified 18 patients correctly with a success rate of 85.71%.

Conclusion: The CAD equipped with the EM segmentation and C4.5 DT classification was successfully distinguished as benign and malignant breast tumor on MRI.

Keywords: Breast lesions, breast cancer, magnetic resonance imaging, computer-aided diagnosis, segmentation

Introduction

The most crucial role in breast cancer treatment is early detection. Mammography is one of the most valuable tools for detecting breast cancer early before physical symptoms appear (1,2). However, mammographic features of early-stage breast cancer cannot be clear and very specific (3). At present, magnetic resonance imaging (MRI) provides superior soft-tissue imaging capability and is considered the most accurate technique for detecting breast cancer (4). However, the interpretation of MRI images is both times consuming and requires an experienced radiologist. At the same time, using breast MRI for screening breast cancer is gradually increasing as well as the MRI is now being used as a screening modality in the high-risk women population (5). Also, the use of MRI is directly or indirectly associated with higher costs. One reason for the higher price is that the long acquire time of the standard protocol currently used and the length of the reading time. A typical MRI study includes thousands of images (6).

In recent years, machine learning and computer-aided techniques are increasingly gaining performance in radiology. To reduce operator dependency and achieve

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greater accuracy, the computer-aided diagnosis (CAD) system is becoming a useful tool for detecting noninvasively and determining tissue characterization in medical images, which leads to an image-based diagnosis. In this way, CAD becomes a necessary tool to help radiologists not only detect tumors but also interpret lesions and avoid unnecessary breast biopsies (7,8).

The CAD, which is seen as the second reader in the clinic, needs to be developed further. The CAD has four main modules: pre-processing, segmentation, feature extraction and selection, and classification (9). Image segmentation is the most important module. There are numerous mass segmentation studies in the literature, but studies on breast segmentation are limited, particularly on breast MRI images (10). One of the segmentation methods, the expectation-maximization (EM) method, has been used for breast density estimation before (11). The most used classifier in literature is k-nearest neighbors (KNN) and supports vector machines (SVM). However, studies with decision trees (DT), linear discriminant analysis (LDA), and naive bayes (NB) as a classification algorithm with MRI are less seen (12).

In this study, a recent user-independent time-saving CAD to diagnose breast cancer using MRI images was presented. Here, we aimed to find the best method for the discrimination of benign and malignant breast masses by comparing the classification methods (LDA, NB, DT) and using EM for segmentation, which has been an unused segmentation on breast MRI images until now.

Methods

Study Design

The present study was approved by the Kayseri City Hospital of Medicine Ethics Committee (number; 2020/73) and conducted between form January 2018 to January 2019 in accordance with the Helsinki Declaration. Consent form was filled out by all participants.

In the study, we used a dataset of 105 breast MRIs randomly selected from our breast department's archive, which includes both benign and malignant lesions. Patients with multiple lesions in the breast MRI, infection, granulomatous mastitis, and patients that their MRI was not enough enchantment for image analysis were excluded from the study. All lesions were verified histopathologically by sonographic guidance using a 14-gauge automatic core-needle biopsy.

All breast MR imaging studies were performed using a 1.5-Tesla MRI (Achieva, Philips, The Netherlands) unit with the patients in a prone position using dedicated eight-channel breast coils. Breast MRI images were obtained as standard with fat suppression FATSET in axial plane using T1 turbo spin-echo sequence. T2W STIR, Contrast examinations (DCE-MRI) were obtained with T1 FATSET and THRIVE sequences in the axial plane. Subtraction images were obtained automatically by the device.

Image Analysis

Pre-processing: A single slice from each MRI image in which the tumor was the most clearly seen in the contrast-enhanced sequence was selected as the representing image for the corresponding MRI image. Then, the noise of the image was reduced using the median filter, Gauss filter and the "top hat and bottom hat" methods. In this way, the picture became brighter and the contrast between the two colors was increased.

Segmentation: The EM algorithm (13) was used for segmentation, which is one of the most critical steps of image analysis. First, an elliptic curve placed on the tumorous region on the image manually. The entire lesion was included in the curve. The segmentation process was applied to the area within the curve, each corresponded to a single region of interest (ROI). At the end of the segmentation process, a total of 105 ROI was obtained from a total of 105 MRI images, and they formed the dataset. Each ROI has only two colors, white and black. The tumor tissue was determined as white and non-tumor tissue as black. Moreover, the tumor boundaries were clarified correctly.

2D Discrete Wavelet Transforms: Each of the segmented images were applied to a 2D-discrete wavelet transform before the texture analysis. Then, these filter results were again passed through low and high pass filters using the same filter coefficients and repeated sample reduction was performed.

Feature Extraction: The intensity-based statistical (histogram) and texture matrix-based features [Gray level co-occurrence matrix, (GLCM)] families were used.

Feature Selection: Random forest (RF) was used for feature selection and the Gini index was used as the feature selection property.

Classification Algorithms: The dataset was randomly splatted into two distinct data sets, such as 80% training set (84 patient's images) and 20% test set (21 patient's images) for training and testing purposes (Table 1).

Three different classification algorithms (DT, NB and LDA) were employed for classification. C4.5 DT was used. The DT generated by C4.5 can be used for classification, and therefore C4.5 is often referred to as a statistical classifier and a benchmark DT program.

Table 1. Patient distribution in the training and testing data sets

	Malign (n=53)	Benign (n=52)
Training group, n (%)	44 (83%)	40 (77%)
Testing group, n (%)	9 (17%)	12 (23%)

Statistical Analysis

The correlation between the two groups of datasets was evaluated by the Pearson correlation matrix.

Results

The dataset was composed of 105 breast MRI (53 malignant, 52 benign). The mean age was 41.40±10.93 years (age range, 18-66 years) for benign lesions, 48.40±11.32 years (age range, 28-81 years) for malignant lesions. The lesion's sizes were between 16.57±4.93 mm (10-30 mm) for benign lesions, 31.03±18.00 (7-85 mm) for malignant lesions. The demographic features of the patients were summarized in Table 2.

Image Analysis Results

The original image in Figure 1a was preprocessed. Then, as the ROI, an elliptic region in Figure 1b, which contained the entire tumorous region, was selected. Later, the ROI was applied to additional preprocessing procedures to obtain the image in Figure 1c. The final image (Figure 1d) was segmented.

The segmented images were applied to the 2D-discrete wavelet transform. After that, four colored images (cD, cH, cV, and cA) were created as a result of texture analysis. Nine different features were extracted from the four colored images. Figure 2 shows feature importances. The plot has shown that the four features we used were more informative and the rest were less informative.

Table 2. Demographic features of the patients

	Malign (n=53)	Benign (n=52)
Age (mean ± SD)	48.40±11.32	41.40±10.93
Size (mm) (mean ± SD)	31.03±18.00	16.57±4.93
Malign n (%)		
Invasive ductal carcinoma	35 (66%)	-
Lobular carcinoma	6 (11.3%)	-
Ductal carcinoma in situ	12 (22.6%)	-
Benign n (%)		
Fibroadenomas	-	42 (80.7%)
Sclerosing adenosis	-	7 (13.4%)
Intramamarian lymph node	-	2 (3.8%)
Lactation adenoma	-	1 (1.9%)

SD: Standard deviation

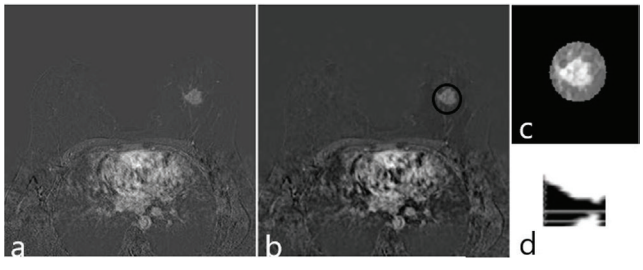

Figure 1. (a) Original image, (b) Preprocessed image and selected ROI, (c) Preprocessed ROI, (d) Segmented ROI
ROI: Region of interest

Classification Performance

Table 3 shows the output as the confusion matrix. According to the table, C4.5 DT ranked 20 patients properly (95.24% success rate). Only one patient is misclassified. NB properly categorized 19 patients (90.48% success rate). LDA accurately categorized 18 patients (85.71% success rate). The C4.5DT algorithm is more accurate than the others.

Discussion

Advances in both imaging and computers have synergistically led to a rapid rise in the potential use of image processing techniques (14). We know that images are more than pictures; they are data. Radiologists have started to show great interest in the clinical use of this data. Images are converted to high-dimensional data and used in decision support of precision medicine (15). The most important limitations are the lack of efficient and standardized systems of feature extraction and

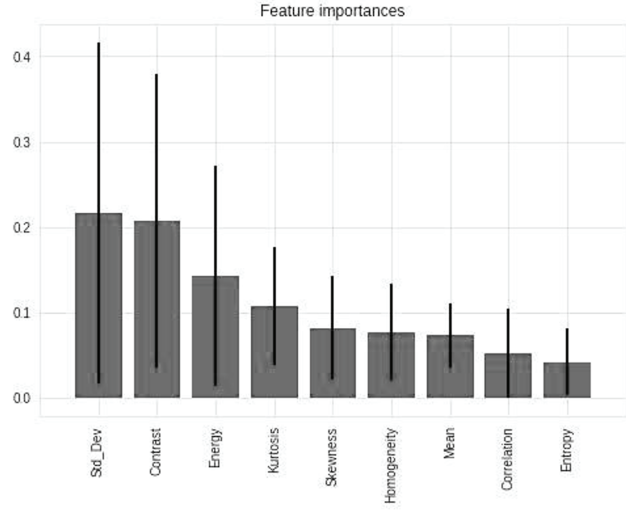

Figure 2. Feature importances

Table 3. Classification report

	C4.5		NB		LDA	
	True	False	True	False	True	False
True	12	0	11	1	10	2
False	1	8	1	8	1	8
Mean AUC	0.80		0.79		0.60	
Precision	1.0		0.88		0.80	
Accuracy (%)	95.2		90.4		85.7	

AUC: Area under curve, NB: Naive bayes , LDA: Linear discriminant analysis

data exploring (16,17). Nevertheless, in comparison with mammography and ultrasound, relatively few CAD systems have been developed for breast MRI in the literature (16,18).

The CAD consists of two major steps: analysis and diagnosis. The analysis step comprises a series of procedures such as preprocessing, segmentation and feature extraction. The diagnosis stage includes the classification procedure (19). Along with the segmentation, the classification module is regarded as the heart of the CAD (20).

Accurate segmentation of the ROI is the largest challenge when analyzing MRI. Most existing breast segmentation methods are semi-automatic and have a limited ability to obtain accurate results. Automatic image segmentation is one of the most difficult processes in image processing. The reason is that the difficulties of removing bookmarks from noisy MRI and intensity inhomogeneity are a common problem within breast MRIs (21). Various techniques have been reported in the documentation of segmentation methods. The most commonly used method is the k-means clustering method (22). The performance of the methods relies on the contrast between the border regions (21,23). It should be remembered that there is no universal segmentation method that can be applied to all images, and no segmentation method is perfect. In other words, as in image enhancement and restoration problems, the methods designed for image segmentation and the performance of these methods are varies depending on the appearance and application. For the first time in the breast MR literature, we used the EM method to segment the ROI, which is the crucial stage in CAD. EM is a popular iterative improvement algorithm for segmentation and model-based auditing method. Recently, studies showed that EM provides a good balance of image quality between low - and high-frequency features and determining the structure of the model and the parameters (24). The iteration alternates between performing an expectation (E) and maximization (M) for each parameter (25). The EM algorithm has previously been used in various modalities for breast cancer but was not used in breast MRI images. With EM, instead of dividing pixels into classes, it is possible to determine the number of components and estimate the mixture. Therefore, we used the EM algorithm to obtain a better image quality in the segmentation phase. In literature, the EM algorithm is known as one of the methods that can be calculated easily and efficiently (26). EM, which is used to cluster data sets that contain categorical and numerical features, was used considering that it would increase the estimated rate on MRI images including benign and malignant mass features. Because compared to other iterative techniques, EM's statistical point of view modeling ability and to obtain the maximum likelihood estimation are stronger (27). In this way, this algorithm revealed the difference between benign and malignant mass features more clearly than we expected.

The feature extraction process is a dimension reduction process. The complexity of data is reduced to simpler data. Accurate feature extraction and appropriate system design are the factors that influence the success and performance of the result (28). Many feature selection techniques are frequently used now. Like the segmentation methods and classifiers, it is impossible to say which is the best algorithm for feature selection or extraction. It all depends on your application at hand (29). DT are algorithms that commonly used for classification and prediction. Classification is the most essential technique in data mining and widely used in various fields (30). Classification of data using the DT technique is a two-step process, which is training and testing. Training step, previously known training data is analyzed by the classification algorithm in order to create a model. In the testing step, test data are used to determine the accuracy of the classification rules or DT. If the accuracy is acceptable, the rules are used to classify new data (30). The most commonly used methods are KNN and SVM as classifiers (31). In addition to these, Yassin et al. (12), in their detailed review of the breast cancer literature, indicate that two studies use LDA and NB, while no studies use DT as their classification algorithm. C4.5 Algorithm is one of the most well-known DT algorithms. The purpose of these calculations is to determine the predictor class that provides the highest information. C4.5 DT classification was used as a CAD approach in our study and achieved a success rate of 95.24% in the differentiation of breast lesions. These three classification methods we used were similar in malignant lesions, but C4.5 was better in discrimination of the benign lesions. The size of the benign lesion was smaller than the malignant lesions and the contrast enhancement patterns were more variable. Therefore segmentation was more difficult in benign lesions. This result showed that the success rate of C4.5 could be increased with the use of EM. However, due to the small number of cases in the test group, statistically significant results could not be obtained.

Study Limitations

We had a small sample size, was not a large independent data set. Image analysis was performed from 2D images. However, some studies have shown that the results are similar in 2D and 3D image analysis. The manual placement of the ROI was also a limitation. Recently, automated software is available for ROI placement (32). Also, the large tumor size of the patients facilitated the detection and recognition of the tumor. Finally, Although a

large number of data statistics and image post-processing restrictions, we achieved satisfactory results. We need to expand our findings in future studies.

Conclusion

Detecting and characterizing breast cancer can be assisted by using some computerized feature extraction and classification algorithms. Malignant tumors can be distinguished from a benign tumor on MRI with 95.24% accuracy using EM segmentation and C4.5 classification. The number of unnecessary biopsies might be reduced with integration into the clinical workflow.

Authorship Contributions

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

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Original Article

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The Relationship Between Pain and Psychological and Cognitive Status in Patients with Acute Low Back Pain: A Cross-Sectional Study

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Abstract

Aim: Low back pain can lead to depression and anxiety as a result of reduced quality of life. Also, catastrophizing can aggravate the pain. Therefore, we aim to investigate the relationship between the severity of acute low back pain and the psychological states of the patients.

Methods: This cross-sectional study involved 168 patients of both genders who applied to the Neurosurgery Outpatient Clinic at the Recep Tayyip Erdogan University Training and Research Hospital between December 2020 and February 2021. Pain severity was assessed with the numerical pain rating scale (NPRS), pain catastrophizing by pain catastrophizing scale (PCS). While evaluating depression and anxiety, beck depression inventory (BDI) and beck anxiety inventory (BAI) were used, respectively.

Results: A statistically significant difference was found in the variance analysis of pain intensity and catastrophizing according to depression symptoms ($p<0.001$). It was also observed that the difference in pain severity and catastrophizing according to anxiety symptoms was statistically significant ($p<0.001$). There was a statistically significant correlation among the BDI, BAI, NPRS and PCS ($p<0.001$).

Conclusion: The findings of our study showed that there is a significant relationship between anxiety, depression, and catastrophizing, and low back pain. Therefore, it is important to consider the psychological state of the patient during the treatment process.

Keywords: Low back pain, psychological state, cognitive state, pain rating, pain catastrophizing

Introduction

Low back pain is an important cause of pain, especially in developed and developing countries, and causes serious physical, psychological and economic losses (1). While 80% of people over the age of 40 experience low back pain at least once in their lives, the annual prevalence of low back pain in the society varies between 3515% (2). According to the Turkish Statistical Institute's data evaluated in 2016; It is seen that the incidence of low back pain, lumbar hernia and other lumbar defects in society is gradually increasing and its incidence has reached 27.1% (3). The World Health Organization estimated the depression rate to be 4.4% and the anxiety disorder rate to 3.6% worldwide in 2015 (4). It is reported that these rates are higher in individuals who experience pain and whose quality of life is adversely affected (4).

In addition to being an uncomfortable condition for the person, pain can disrupt the person's quality of life and trigger anxiety and depression unless it is treated (5). Besides physical discomfort, anxiety and depression itself can also cause disability (4,6). Pain tolerance and response pattern varies from person to person. While psychological factors may have an effect on this reaction, the pain itself can lead to psychological problems (7,8).

In addition to depression and anxiety, patients' tendency to catastrophizing has been shown to cause pain to be perceived stronger than it actually is (9,10). Catastrophizing has been defined as "thinking about the worst possible outcome of incidents and threats and increasing the likelihood of experiencing this bad outcome". Based on this definition, the pain catastrophic

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scale (PCS) was developed by Sullivan et al. (11) to assess the severity of personal disaster.

In our study, we aimed to investigate the relationship between the severity of pain in patients with acute low back pain and the patient's cognitive state (catastrophizing pain), and psychological state (depression and anxiety severity).

Methods

Study Design

This prospective cross-sectional study was conducted in accordance with the Declaration of Helsinki and approved by the institution's Ethics Committee (decision number: 2020/248 decision date: 23.12.2020). Proposals were made to 209 patients for the study, and 18 of 186 patients who agreed to participate in the study were excluded from the study because they did not meet the specified criteria. Therefore, the sample consisted of 168 male and female participants who applied to Recep Tayyip Erdogan University Training and Research Hospital's Neurosurgery Outpatient Clinic with the complaint of mechanical back pain between December 2020 and February 2021. Patient written informed consent was obtained after it was reported that the study would not impact patient treatment and the study protocol was announced.

History of alcohol and substance use, inability to cooperate, and disapproval of participation in the study were determined as exclusion criteria for the study. There was a total of 41 patients, including 21 who refused to participate in the study and 18 who did not meet the criteria for the study (n=41).

Patients were informed about the study and those who accepted to participate in the study were directed to the service, and a neurosurgeon who has the necessary knowledge about the study subject and scales was informed about each patient's age, gender, body mass index, educational status, marital status, existing comorbidities (hypertension, diabetes mellitus), ischemic heart disease, chronic obstructive pulmonary disease, depression, anxiety etc.) have been recorded.

Pain severity was assessed using the numerical pain rating scale (NPRS) (12) and pain catastrophizing by PCS (11). The tools used to evaluate the depression and anxiety levels of the participants are the beck depression inventory (BDI) (13) and the beck anxiety inventory (BAI) (14), respectively.

Numeric Rating Scale for Pain (NPRS)

The severity of low back pain was evaluated with the Numeric Rating Scale for Pain (zero equals no pain, ten equals maximum pain). The scale is a reliable method that evaluates subjective pain intensity, does not require literacy skills, can be applied easily, and is accepted in the literature (12).

Pain Catastrophizing Scale (PCS)

Pain catastrophizing severity which was developed by Sullivan et al. (11) in 1995 using the Pain Catastrophizing Scale is used to determine the catastrophe of pain. The reliability and validity study of the Turkish version of the scale was conducted by Süren et al. (15). The scale consists of 13 questions and has three subscales: rumination, magnification and helplessness. Each question is scored between zero and four. The total score to be obtained from the scale varies between zero and 52 while high scores indicate negative results. In many countries, its validity and reliability have been studied (16).

Beck Depression Inventory (BDI)

The scale that is developed by Beck et al. (13) consists of 21 questions and the questions are scored between zero and three. The scores increasing from zero to three in this scale are proportional to the severity in the evaluated parameter. The highest score to be obtained from the scale is 63. For the Turkish society, 17 points obtained from the BDI were determined as the cut-off point for moderate and severe depression. The validity and reliability of BDE in Turkish society was studied by Hisli et al. (17).

Beck Anxiety Inventory (BAI)

The 21-question scale that is developed by Beck et al. (14) assesses the severity of anxiety. Each question is scored between zero and three. The total score ranges from zero to 63. Higher scores are consistent with anxiety severity. For the Turkish society, 16 points received from the BAI have been determined as the value that distinguishes high anxiety levels. The validity and reliability of BAI in Turkish society were studied by Ulusoy et al. (18).

Statistical Analysis

The statistical analysis of the data was performed with the SPSS for Windows 22 (SPSS, IBM, Chicago, IL, USA) package program. Frequencies, percentages, means and standard deviations are given for socio-demographic variables. Data on continuous variables are given as mean standard deviation. Variables with more than two categories were analyzed by analysis of variance. When a significant difference was detected as a result of analysis of variance, the post-hoc Tukey test was applied to determine which groups the difference was due to, and Bonferroni correction was made. Pearson correlation analysis was conducted to evaluate the relationship between NPRS and PCS scores with depression and anxiety scores. In general, statistical significance was accepted as $p<0.05$ in the tests. The p-value $<0.05/6=p<0.008$ for post-hoc Tukey with Bonferroni correction was considered statistically significant.

Results

168 patients (Female: 71, Male: 97) who met the study criteria among the patients who applied to the Recep Tayyip Erdogan University Training and Research Hospital's Neurosurgery Outpatient Clinic with the complaint of low back pain were included in the study. The mean age and standard deviation were 46.81±11.81. The mean pain duration and standard deviation were 2.54±1.24. Socio-demographic information is provided in Table 1. In the Lasegue test, 106 of the participants were positive (LP) and 62 of them were negative (LN). When the magnetic resonance (MR) findings were evaluated, it was seen that there were 83 people without radiological findings or bulging, 40 people with protrusion and 45 people with extrusion and sequestration (Table 2). To the findings, the pain intensity has a positive correlation of 0.60 with pain catastrophizing (r=0.60), has a positive correlation with anxiety (r=0.59) and has a positive correlation with depression (r=0.60). There was a 0.54 positive correlation (r=0.54) between pain catastrophy and anxiety, and a positive correlation (r=0.60) between pain catastrophy and depressive symptoms (Table 3).

A significant difference was found between the groups (F: 26.46; p<0.001) (Table 4), when the participants were divided into four groups as minimal, mild, moderate and severe according to their depression symptoms and analysis of variance was performed in terms of their NPRS scores. Table 5 presents the results of the post-hoc test used to identify the binary group that was the source of the statistically significant difference. When these four groups were compared in terms of PCS scores, a significant difference was found between the groups (F: 31.25; p<0.001) (Table 4). The results of the post-hoc test for the relevant variance analysis are shown in Table 5.

Table 1. Socio-demographic characteristics of the sample

	n (%)
Gender	
Female	71 (42.3)
Male	97 (57.7)
Marital status	
Single	27 (16.1)
Married	141 (83.9)
Education	
Illeterate/Less than primary school	87 (51.8)
Primary school	63 (37.5)
Middle school/High school	13 (97.7
College/University	5 (3.0)
Age	Mean ± Standard deviation
	46.81±11.81

When the participants were divided into four groups as low, mild, moderate, and severe according to their anxiety symptoms, and analysis of variance in terms of NPRS scores, a significant difference was found between the groups (F: 30.17; p<0.001) (Table 6). The post-hoc test performed to determine the statistically significant difference arises from the difference between the two groups is given in Table 7. When these four groups were compared in terms of PCS scores, a significant difference was found between the groups (F: 23.50; p<0.001) (Table 6). The results of the post-hoc test for the relevant variance analysis are presented in Table 7.

Discussion

In some of the cases presenting with the complaint of acute low back pain, limiting straight leg raising (Lasegue sign) and lumbar MRI findings from sciatica stretching tests performed in physical examination do not correspond to the severity of the perceived pain. In our study, we had a significant proportion of patients who had negative Lasegue sign (62 people) and/or who did not have any pathology in lumbar MR imaging (24 people). In various studies, the positivity of Lasegue sign was found to be between 57-90% in patients with low

Table 2. Clinical features of the cases

	n (%)
Physical examination finding	
Lasegue negative	62 (36.9)
Lasegue positive	106 (63.1)
MR findings	
No finding	24 (14.3)
Bulging	59 (35.1)
Protrusion	40 (23.8)
Extrude	40 (23.8)
Sequester	5 (3.0)
Depression	
Minimal	59 (35.1)
Mild	46 (27.4)
Moderate	48 (28.6)
Severe	15 (8.9)
Anxiety	
Low	73 (43.5)
Mild	39 (23.2)
Moderate	23 (13.7)
Severe	33 (19.6)
Pain duration (week)	Mean ± Standard deviation
	2.54±1.24

MR: Magnetic resonance

Table 3. Correlation between parameters

		Pain duration	NPRS	PCS	BAI	BDI
Pain duration	r	1	-0.142	-0.015	-0.149	-0.132
	p	-	0.067	0.852	0.055	0.088
NPRS	r	-0.142	1	0.604**	0.596**	0.603**
	p	0.067	-	0.000	0.000	0.000
PCS	r	-0.015	0.604**	1	0.540**	0.599**
	p	0.852	0.000	-	0.000	0.000
BAI	r	-0.149	0.596**	0.540**	1	0.861**
	p	0.055	0.000	0.000	-	0.000
BDI	r	-0.132	0.603**	0.599**	0.861**	1
	p	0.088	0.000	0.000	0.000	-

r: Pearson correlation coefficient, p: p value, ** p<0.01 significance level, NPRS: Numerical rating scale for pain, PCS: Pain catastrophizing scale, BAI: Beck anxiety inventory, BDI: Beck depression inventory

Table 4. Analysis of variance of pain intensity and catastrophizing according to depression symptoms

		Sum of squares	df	Mean square	F*	p
NPRS	Between groups	187.452	3	62.484	26.466	<0.001
	Within groups	387.191	164	2.361	-	-
	Total	574.643	167	-	-	-
PCS	Between groups	9684.575	3	3228.192	31.250	<0.001
	Within groups	16941.401	164	103.301	-	-
	Toplam	26625.976	167	-	-	-

*One-way ANOVA, NPRS: Numerical rating scale for pain, PCS: Pain catastrophizing scale

Table 5. *Post-hoc analysis of depression groups in terms of pain severity and catastrophizing

Dependent variable	Comparison groups for depression	Mean difference	p	95% Confidence interval	
				Lower	Upper
NPRS	Minimal-low	-1.05527*	0.003	-1.8397	-0.2708
	Minimal-moderate	-2.27719*	<0.001	-3.0524	-1.5020
	Minimal-severe	-2.94802*	<0.001	-4.1013	-1.7948
	Mild-moderate	-1.22192*	0.001	-2.0448	-0.3990
	Mild severe	-1.89275*	<0.001	-3.0786	-0.7069
PCS	Minimal-mild	-14.54273*	<0.001	-19.6705	-9.4149
	Minimal-severe	-18.68023*	<0.001	-26.3086	-11.0519
	Mild-moderate	-14.53351*	<0.001	-19.9767	-9.0904
	Mild-severe	-18.67101*	<0.001	-26.5148	-10.8272
	Moderate-severe	-10.39526*	0.002	-17.9074	-2.8831

*Tukey test, NPRS: Numerical rating scale for pain, PCS: Pain catastrophizing scale, statistical significance level: p<0.008, (Only statistically significant comparisons are presented)

back pain (19,20). In our study, although the Lasegue test was found to be positive in 106 of 168 cases with low back pain complaints (63%), in 62 of these cases, moderate and severe herniation findings (protrusion, extrusion and sequestration) were detected in radiology. This finding suggests that other factors besides pathology also contribute to the perception of pain severity. As a matter of fact, the psychosocial aspect of low back pain is emphasized as well as its biological aspect (21-23).

Since pain is a subjective symptom, various measurement tools have been developed for grading. NPRS is one of the tools used for pain grading and is used to assess pain in other pain types such as low back pain (12,24) The positive correlation between pain severity and anxiety and depression levels is one of the important findings of our study. It has been shown that low back pain is associated with depression (25-27) and it has been stated that depression may have a negative effect on the

Table 6. Variance analysis of pain severity and catastrophy according to anxiety symptoms						
		Sum of squares	**df**	**Mean square**	**F***	**p**
NPRS	Between groups	204.375	3	68.125	30.174	<0.001
	Within groups	370.268	164	2.258	-	-
	Total	574.643	167	-	-	-
PCS	Between groups	8006.936	3	2668.979	23.509	<0.001
	Within groups	18619.040	164	113.531	-	-
	Total	26625.976	167	-	-	-
*One-way ANOVA, NPRS: Numerical rating scale for pain, PCS: Pain catastrophizing scale						

Table 7. *Post-hoc analysis of anxiety groups in terms of pain severity and catastrophizing					
Dependent variable	**Comparison groups for anxiety**	**Mean difference**	**p**	**%95 Confidence interval**	
				Lower	**Upper**
NPRS	Low-moderate	-1.90232*	<0.001	-2.8349	-0.9698
	Low-severe	-2.83645*	<0.001	-3.6545	-2.0184
	Mild- severe	-2.02331*	<0.001	-2.9458	-1.1009
PCS	Low- severe	-17.81694*	<0.001	-23.6182	-12.0157
	Mild- severe	-16.86014*	<0.001	-23.4015	-10.3188
	Moderate- severe	-10.39526*	0.002	-17.9074	-2.8831
*Tukey test, NPRS: Numerical rating scale for pain, PCS: Pain catastrophizing scale, statistical significance level: p<0.008, (Only statistically significant comparisons are presented)					

prognosis of low back pain (28). In various studies, it has been shown that those with severe pain have more severe psychological distress (29,30). The relationship between pain intensity and depression and anxiety is also observed in rheumatoid arthritis (31), headache (32), and gastrointestinal system disorders (33). Bener et al. (34) compared 1,290 low back pain patients with a control group of 890 people and found that anxiety and depression levels were higher in the low back pain group. It is understood that these findings are in parallel with the literature. On the other hand, in a twin study, it was suggested that the relationship between low back pain and depression may be due to familial genetic factors rather than causation (35).

In addition to the relationship between pain and depression and anxiety, disastrous pain is also of great importance in the perception of pain. It has been reported that disastrous pain is one of the psychological factors that cause the person to perceive the intensity of pain more than it really is. In a study conducted to evaluate these psychological factors, lower PCS scores were found in patients who received training before lumbar surgery (36). It has been shown that informing about the pain may cause a decrease in the PCS scores or may have a positive change in the radiological findings (37). It has also been shown that catastrophizing plays an important role in modulating postoperative pain in patients who have undergone spine surgery and used PCS (38). Disaster is actually used as a coping strategy. It has also been found that catastrophizing is associated with disability and delayed recovery as well as pain (39). In a study in which half of the participants were found to be highly catastrophic, it was found that disastrous pain was associated with more severe pain (40). In our study, higher NPRS scores were found in those with higher PCS scores.

Study Limitations

The absence of a control group in our study can be considered as a limitation. Determining the frequency of anxiety and depression symptoms in the control group without low back pain could have contributed to the study.

Conclusion

The study findings showed that there is a significant relationship between psychological and cognitive state and low back pain. Low back pain may also be one of the symptoms of somatization in depression, and some depressed patients may be admitted to the hospital with low back pain. Depression and anxiety can lower the pain threshold or, conversely, aggravate existing depression and anxiety. In addition, low back pain can lead to disability, as well as existing or developing anxiety and depression alone can lead to disability. Therefore, patients with low back pain should be handled in a detailed and versatile way and the treatment plan should be made in the light of this information.

Authorship Contributions

Concept: O.E.B., Design: O.E.B., Data Collection or Processing: B.O., Analysis or Interpretation: B.O., Literature Search: O.E.B., Writing: O.E.B.,

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Evaluation of Relationship Between Tp-E Interval Values and QT Dispersion in Electrocardiogram in Children With B12 Vitamin Deficiency

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Abstract

Aim: B12 vitamin deficiency may cause cardiac autonomic dysfunction, heart rate variability, endothelial dysfunction and subclinical atherosclerosis, a significant degree of reduction in heart ejection fraction and deformation of the left ventricular myocardium. We aimed to investigate the effect of B12 deficiency in children on cardiac electrical activity by comparing the Tp-e and QT dispersion values between healthy children and children with B12 deficiency.

Methods: The demographic data, laboratory results electrocardiography and echocardiography results of isolated B12 patients (n=64) with vitamin B12 deficiency and control group (n=64) included in the study between 15.3.2020 and 15.06.2020 were prospectively recorded and comparatively analyzed.

Results: A total of 128 patients included in the study. Corrected QT (QTc) value and Tp-e interval, were statistically significantly higher in the patient group ($p<0.05$). Tp-e/QT and Tp-e/QTc ratios in the patient groups were statistically significantly higher than the ones in the control group ($p<0.05$).

Conclusion: Repolarization differences in B12 deficient children when compared to those of healthy children, might reflect subclinical symptoms.

Keywords: Child, vitamin B12 deficiency, QT dispersion, repolarization, Tp-e interval

Introduction

B12, a water-soluble vitamin, acts as a coenzyme in the synthesis of DNA required for cell division and proliferation, myelinization of neuronal cells and in the metabolisms of lipids and carbohydrates. By affecting the activity of the sympathetic and parasympathetic system, vitamin B12 deficiency causes heart rate variability and cardiac autonomic dysfunction and also results in endothelial dysfunction and subclinical atherosclerosis with its role in cellular metabolic pathways inhibiting homocysteine metabolism, lipid peroxidation and free radical formation. There are studies where vitamin B12 deficiency is associated with left ventricular myocardial deformation (1,2).

Left ventricular dysfunction plays a key role in the development of arrhythmias. Prolonged QT interval increases the sensitivity of the heart to ventricular arrhythmias. The QT dispersion and Tp-e interval values are recognized as an indicator for ventricular repolarization. (3,4). Prolonged QT dispersion and Tp-e interval values indicate a predisposition to ventricular arrhythmias.

In the literature, several studies show that vitamin B12 deficiency causes cardiac autonomic dysfunction and subclinical atherosclerosis in the pediatric age group (1,5). Autonomic dysfunction caused by vitamin B12 deficiency and cardiac dysfunction secondary to anemia, its role in pathways preventing the formation of free radicals, its effect on endothelial reconstruction and the associated cardiac complications may make the heart susceptible to arrhythmias (6-8).

In our study, we aimed to investigate the effect of vitamin B12 deficiency on cardiac electrical activity in children by comparing Tp-e interval and QT dispersion values of children with isolated vitamin B12 deficiency to Tp-e interval and QT dispersion values of healthy children.

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Methods

Study Design

Ethical committee approval was obtained for our study from the Istanbul Training and Research Hospital, Clinical Research Ethics Committee of our hospital with the decision numbered 2020-06 and dated 11/03/2020. The families were informed about the study and their written consents were obtained.

Patients only with vitamin B12 deficiency were included in the study from among children who do not have any chronic disease (hypertension, diabetes mellitus, congenital or acquired heart disease, thyroid disease, chronic lung, liver and kidney disease, etc.) and whose other vitamin values (vitamin D, folate and ferritin) are in the normal range. The control group comprised of patients whose all vitamin values, including vitamin B12, were normal, and who did not have any additional chronic diseases and applied to the Pediatric Cardiology Outpatient Clinic for a routine pediatric examination or report for making sports and were not found to suffer from any problem and did not take any medication.

The demographic data of the patients were obtained from the patient files and the hospital information management system. Physical examinations, blood tests (hemogram, glucose, urea, creatinine, upper, lower, electrolytes, vitamin B12, folate, 25-OH vitamin D, ferritin, iron, iron-binding capacity, T4 TSH), age, gender, electrocardiography (ECG) and echocardiography (ECO) findings of the patients (taken prior to the initiation of the vitamin B12 deficiency treatment) between 15.3.2020 and 15.06.2020 were recorded prospectively in our clinical data registry form.

Electrocardiogram Assessments

Their ECGs were assessed by the same pediatric cardiologist. ECGs were taken by a 12-lead device (Schiller Cardiovit At-102 plus) with velocity 25 mm/sec and amplitude 10 mm/mV. A magnifying glass and a manual ruler were used during the examination of ECG samples in order to increase the sensitivity of P wave, PR interval, QRS complex, QT interval, Corrected QT (QTc), Tp-e, Tp-e/QT, Tp-e/QTc, QT dispersion, and QTc dispersion calculations. The waves and intervals measured in our study are shown in Figure 1.

Echocardiographic examinations were performed with 2-dimensional and color Doppler echocardiography device (GE Vivid S5®). Echocardiographic assessment of all cases included in the study was performed by the same experienced pediatric cardiologist. In all cases, classical echocardiographic measurements, i.e., left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), end-diastolic interventricular septal diameter (IVSd), end-diastolic left ventricular posterior wall diameter (LVPWd), ejection fraction (EF) and shortening fraction (SF) measurements were made.

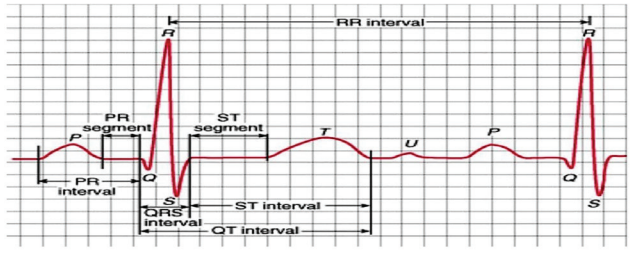

Figure 1: Waves and intervals making up the ECG
ECG: Electrocardiography

Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics: Categorical variables are expressed in numbers and percentages and numerical variables are expressed in mean, standard deviation, minimum and maximum values. When the numerical variables met the normal distribution condition, the Student's t-test was used for the comparison of two independent groups, and the Mann-Whitney U test was used when the normal distribution condition was not met. In independent groups, the rates were compared by chi-square test. The relationships between numerical variables were analyzed with Pearson's correlation analysis when the normal distribution condition was met, and when the normal distribution condition was not met, Spearman correlation analysis was used. The significance level alpha was accepted $p<0.05$.

Results

A total of 128 patients (64 patients and 64 controls) were included in the study. Of the 64 patients included in the study, 33 (51.6%) were female and 31 (48.4%) were male. The control group consisted of 33 (53.9%) girls and 31 (48.4%) boys. No statistically significant difference was found between the two groups in terms of gender distribution ($p=1$). The mean age of the patient group was 11±2.7 years and the mean age of the control group was 10.8±2.3 years. No statistically significant difference was found between the patient and control groups in terms of the mean age ($p=0.428$).

In the patient group, the mean vitamin B12 level was 144±30.3, whereas in the control group, the mean vitamin B12 level was 310.6±131.9. Folate level was found to be statistically significantly lower in the patient group compared to the control group ($p=0.035$). However, it remained in the range of normal values in both groups (Table 1).

When all cases were evaluated, a weak positive correlation was found between vitamin B12 level and white

Table 1. The distribution of vitamin and iron variables of the patient and control groups

	B12 deficiency group		Control group		
	Mean ± SD	Minimum to maximum	Mean ± SD	Minimum to maximum	p
Vitamin B12 (180-914 (pg/mL)	144.0±30.3	50-191	310.6±132	200-862	<0.001[a]
Folate (5.9-24 ng/mL)	10.0±2.8	4.69-17.68	11.1±2.9	5.21-18.2	0.035[b]
Ferritin (11-316 ng/mL)	23.5±7.4	12-49.6	27.3±13.1	11.7-79.6	0.179
TIBC1 (250-450 mcg/dL)	285.8±49.1	210-418	283.3±49.2	172-433	0.778
Iron (60-180 mcg/dL)	78.1±26.8	23-170	79.1±26.3	37-160	0.832
25-OH Vitamin D (14-50 ng/mL)	17.1±3.7	12-37.5	18.5±4.3	13.5-33.8	0.079

[a]Student's t-test, there is a significant difference between the groups in terms of vitamin B12.
[b]Student's t-test, there is a significant difference between the groups in terms of folate. TIBC: Total iron-binding capacity, SD: Standard deviation

Table 2. Electrocardiographic findings of the patient and control groups

	B12 group deficiency		Control group		
	Mean ± SD	Minimum to maximum	Mean ± SD	Minimum to maximum	p
Heart rate (minute)	83.8±14.8	54-135	88.1±16.0	59/127	0.118
P (sec)[1]	0.09±0.01	0.07-0.12	0.09±0.01	0.06-0.12	0.835
PR (sec)[1]	0.12±0.01	0.09-0.15	0.12±0.02	0.09-0.16	0.977
QRS (sec)[1]	0.08±0.01	0.07-0.10	0.08±0.01	0.07-0.11	0.877
QT (msec)[2]	327.9±23.2	273-396	328.3±44.7	33-388	0.164
QTc (msec)[2]	393.5±18.8	335-430	405.5±18.7	360-445	<0.001[a]

[1]Second
[2]Millisecond
[a]Student's t-test, there is a significant difference between the groups in terms of corrected QT distances. SD: Standard deviation

blood cell (WBC) and platelet values (r=0.044; r=0.016, respectively). No statistically significant relationship was found between other hemogram parameters and vitamin B12 level (p>0.05). No statistically significant difference was found in laboratory parameters in both groups (p>0.05).

QTc was found to be significantly higher in the group with vitamin B12 deficiency compared to the control group (p<0.001). There were no patients with a QTc value >445 ms in both the patient and control groups (Table 2).

In the patient group, the mean Tp-e interval was found to be 81.4±4.4 ms. In the control group, the mean Tp-e interval was found to be 72.3±6.9 ms. Tp-e interval was found to be statistically significantly higher in the patient group compared to the control group (p<0.001) (Table 3).

In the patient group, the Tp-e/QT ratio and the Tp-e/QTc ratio were found to be statistically significantly higher than the control group (p<0.001 and p=0.001) (Table 3).

QTd and QTcd values were found to be statistically significantly higher in the patient group compared to the control group (p=0.009 and p<0.001) (Table 4). The minimum value of QTc in the patient group was found to be statistically significantly lower than the control group (p<0.001) (Table 4).

No significant difference was found in both groups in terms of EF and SF (p=0.408 and p=0.062). In the patient

Table 3. Comparison of Tp-e interval, Tp-e/QT ratio and Tp-e/QTc ratio in the patient and control groups

	B12 group deficiency		Control group		
	Mean ± SD	Minimum to maximum	Mean ± SD	Minimum to maximum	p
Tp-e	81.4±4.4	68-90	72.3±6.9	56-88	<0.001[a]
Tp-e/QT	0.25±0.02	0.19-0.33	0.22±0.02	0.17-0.27	<0.001[b]
Tp-e/QTC	0.21±0.01	0.16-0.24	0.18±0.02	0.13-0.26	<0.001[c]

[a]Student's t-test, there is a significant difference between the groups in terms of Tp-e interval
[b]Student's t-test, there is a significant difference between the groups in terms of Tp-e interval/QT distance ratio
[c]Student's t-test, there is a significant difference between the groups in terms of Tp-e interval/ corrected QT distance ratio OTc: Corrected QT, SD: Standard deviation

group, IVSd and LVPWd (Left ventricular posterior wall diameter) values were found to be statistically significantly higher than the control group (p=0.013; p=0.040).

A statistically significant negative correlation was found between vitamin B12 level and age in all cases included in the study (r=-0.175) (Table 5). In all cases, a statistically significant negative correlation was found between vitamin B12 level and Tp-e interval, Tp-e/QT, Tp-e/QTc values (r=-0.580; r=-0.511; r=-0.549, respectively) (Table 5).

Heart rate was found to be statistically significantly lower in boys than in girls (p=0.043). In terms of

echocardiography measurements, LVESD (Left ventricular end-diastolic diameter) value was found to be statistically significantly higher in boys compared to girls (p=0.042) (Table 6).

In the control group, heart rate was found to be statistically significantly lower in boys compared to girls (p=0.034). There was no statistically significant difference in other ECG and ECO parameters (p>0.05).

Discussion

In our study, we found that in ECGs of children with isolated vitamin B12 deficiency, QT intervals and Tp-E intervals, which can increase the predisposition to arrhythmia, were statistically significantly prolonged.

Table 4. QT dispersion and QTc dispersion values of the patient and control groups

	Vitamin B12 deficiency group		Control group		
	Mean ± SD	Minimum to maximum	Mean ± SD	Minimum to maximum	p
QT Minimum	315.8±23.8	261-384	321.6±27.3	228-376	0.204
QT Maximum	340.9±25.5	278-418	344.0±24.4	288-400	0.476
QTd	25.8±10.7	7-49	20.8±10.9	4-52	0.009[a]
QTc Minimum	376.8±20.5	326-423	392.8±22.2	341-454	<0.001[b]
QTc Maximum	413.1±19.1	367-453	419.2±17.9	377-460	0.077
QTcd	36.1±13.0	16-79	27.4±14.7	1-69	<0.001[c]

[a]Student's t-test, there is a significant difference between the groups in terms of QT dispersion value
[b]Student's t-test, there is a significant difference between the groups in terms of corrected QT minimum value
[c]Student's t-test, there is a significant difference between the groups in terms of corrected QT dispersion value
OTc: Corrected QT, SD: Standard deviation

Table 5. Evaluation of vitamin B12 levels, age and electrocardiographic findings in all cases

	B12	
	r	p
Age	-0.175	0.048[a]
ECG		
Heart Rate	0.103	0.246
Tp-e	-0.580	<0.001[b]
Tp-e/QT	-0.511	<0.001[c]
Tp-e/QTC	-0.549	<0.001[d]

[a]Pearson correlation, there is a significantly negative correlation between vitamin B12 and age.
[b]Pearson correlation, there is a significantly negative correlation between vitamin B12 and Tp-e interval.
[c]Pearson correlation, there is a significantly negative correlation between vitamin B12 and Tp-e interval/QT distance ratio.
[d]Pearson correlation, there is a significantly negative correlation between vitamin B12 and Tp-e interval/corrected QT distance ratio.
ECG: Electrocardiography, OTc: Corrected QT

By affecting the activity of the sympathetic and parasympathetic system, vitamin B12 deficiency causes heart rate variability and cardiac autonomic dysfunction and also results in endothelial dysfunction and subclinical atherosclerosis with its role in cellular metabolic pathways inhibiting homocysteine metabolism, lipid peroxidation and free radical formation. There are studies where vitamin B12 deficiency is associated with left ventricular myocardial deformation (1,2).

Herzlich et al. (9) found that left ventricular EF was significantly lower in the vitamin B12 deficient patients in the adult group. Kaya et al. (7) report that global and segmental myocardial deformation is impaired in patients with vitamin B12 deficiency and this disorder is associated with vitamin B12 levels.

The autonomic nervous system is the key regulator of the physiological functions of the cardiovascular system. It is known that vitamin B12 deficiency leads to the impairment of neuron myelinization and thus, causes cardiac autonomic dysfunction. In their study that was conducted with a group of patients with B12 deficiency, Beitzke et al. (10) evaluated the hemodynamic and autonomic responses of the patients with the tilt-table test. It was found that the baroreflex response was impaired in the vitamin B12 deficient group and a significant decrease was observed in the blood pressure measured after the tilt table test (10). In the paediatric patient group, the vitamin B12 deficiency was shown to cause the heart rate variability by affecting the activity of the sympathetic and parasympathetic system (2,11). Öner et al. (12) compared low levels of vitamin B12 with the findings of postural orthostatic tachycardia syndrome (POTS) pattern in their study on adolescent children diagnosed with vasovagal syncope. It was reported that the deficiency may cause POTS with sympathetic system baroreceptor dysfunction in children with vitamin B12 deficiency (12).

Vitamin B12 has been associated with endothelial dysfunction and subclinical atherosclerosis with its role in cellular metabolic pathways that inhibit lipid peroxidation and free radical formation (1,6). In their study on the paediatric group with vitamin B12 deficiency, Çelik et al. (1) report a significant relationship between carotid intima-media thickness values measured in the early detection of atherosclerosis and the autonomic modulation of heart rate variability (HRV) (1).

Vitamin B12 deficiency is detected in various chronic diseases that develop with immune and inflammatory processes. Studies show that inflammation-related factors such as oxidative stress, nitric oxide production and exposure to various cytokines are associated with

Table 6. Electrocardiographic and echocardiographic findings by gender in the vitamin B12 deficiency group					
	Male			Female	
	Mean ± SD	Minimum to Maximum	Mean ± SD	Minimum to Maximum	p
ECG					
Heart rate	79.9±11.8	56-107	87.4±16.5	54-135	0.043[a]
QTc (msec)	395±14.8	366-430	391.5±21.9	335-429	0.391
Tp-e	82.4±4.5	68-90	80.5±4.3	72-90	0.084
Tp-e/QT	0.25±0.02	0.20-0.27	0.25±0.02	0.19-0.33	0.320
Tp-e/QTC	0.21±0.01	0.16-0.24	0.21±0.01	0.17-0.23	0.647
ECG					
LVEDD (mm)	43.0±4.9	33-52	40.6±5.0	32-48	0.057
LVESD (mm)	25.7±6.5	17-55	23±3.1	16-31	0.042[b]
EF (%)	74.4±5.6	63-86	73.7±7.3	64-89	0.518
SF (%)	41.7±5.0	34-53	41.9±7.0	34-60	0.549
IVSd (mm)	8.32±1.70	6-11	8.33±1.57	5-11	0.881
LVPWd[6] (mm)	8.32±1.64	6-11	8.33±1.85	4-12	0.908

LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, EF: Ejection fraction, SF: Shortening fraction, IVSd: Interventricular septum diameter, LVPWd: Left ventricular posterior wall diameter, ECG: Electrocardiography, SD: Standard deviation
[a]Mann-Whitney U test, heart rate was found to be statistically significantly lower in boys than in girls (p=0.043).
[b]Mann-Whitney U test, left ventricular end-diastolic diameter value was found to be statistically significantly higher in boys compared to girls

increased intestinal permeability. Increased intestinal permeability is observed in another study conducted on patients with Behcet's syndrome and it is reported that the absorption of folate and vitamin B12 due to subclinical gastrointestinal inflammation may decrease (13). Vitamin B12 prevents oxidative stress with its role in cellular metabolic pathways that inhibit lipid peroxidation and free radical formation (14). In a study where the relationship between rheumatoid arthritis that develops with immune and inflammatory processes and vitamin B is examined, the detection of Th1-immune response and oxidative stress stimulated in parallel with decreased levels of vitamins B suggests that the immune activation may be accountable for homocysteine accumulation (15). Studies have been conducted in the childhood group to evaluate chronic diseases in which immune and inflammatory mechanisms play a role in the pathogenesis and their effects on the electrical activity of the heart. A significant relationship was found between Qt dispersion and Tp-e interval values in patients with Familial Mediterranean Fever, Kawasaki, hypothyroidism, celiac disease, ulcerative colitis and Crohn's disease (16-19).

In the study conducted by Isakov et al. (20) on 120 individuals between the ages of 40-70, one group was administered a multivitamin containing vitamin B12 and the other group was administered placebo for 8 weeks. The blood values and homocysteine levels showed that the cardiovascular risk parameters decreased in the group receiving vitamin supplements (20).

Several ECG parameters provide preliminary information on current or likely clinical situations. QT interval and T wave are significant as they indicate cardiac repolarization. It is shown that the increase in QT dispersion, which is considered to indicate regional heterogeneity in myocardial repolarization, causes serious ventricular arrhythmias and sudden cardiac death by way of re-entry (21). The Tp-e interval corresponds to the ventricular repolarization dispersion. Any increase in ventricular repolarization dispersion is regarded as an important risk factor for ventricular arrhythmias. The prolonged Tp-e interval represents the abnormal dispersion of ventricular repolarization and is associated with an increased risk of ventricular arrhythmia (14). Therefore, the Tp-e interval is a non-invasive screening method for arrhythmogenesis. Tp-e interval, the Tp-e/QT ratio and Tp-e/QTc ratio are parameters that represent the increase in the ventricular repolarization dispersion in recent studies. The prolonged Tp-e interval is associated with increased mortality in patients with long QT syndrome, Brugada syndrome and acute myocardial infarction. Since Tp-e/QT ratio is not affected by the heart rate and body weight, it is a more sensitive marker than others (4).

We could not find any study in the literature in English that evaluates the relationship between vitamin B12 and QT dispersion, which is used as an indicator of susceptibility to ventricular arrhythmia, and Tp-e interval in the adult or paediatric population. However, studies that evaluate these parameters with iron deficiency and vitamin D in the paediatric population are available. Karadeniz et al.

(22) report a significant negative correlation between the level of ferritin and Tp-e interval and QT dispersion values, which was thought to be associated with impaired cardiac hemodynamics due to iron deficiency anaemia. In their study conducted with 100 adolescent patients with the aim of investigating the relationship between vitamin D and ventricular repolarization abnormalities, Bagrul et al. (23) reported that the effects of vitamin D on cardiac contractility and calcium haemostasis of the myocardium and QT dispersion and Tp-e interval values were found to be high. Tp-e interval and the Tp-Te/QT ratio were found significantly increased in patients with ventricular tachycardia and ventricular fibrillation more than other in patients with ventricular premature complexes (VPC) and may be used as a novel non-invasive marker of differentiating malignant and benign VPC (24). In another article, Tp-e interval, Tp-e/QT ratio, and Tp-e/QTc ratio, in patients with newly diagnosed COVID-19, were prolonged compared with normal healthy individuals (25). Our study suggests that both autonomic nervous system dysregulation and its function in cellular metabolic pathways and its endovascular damaging effects result in changes in the cardiac electrical activity.

In our study, QT dispersion and QTc dispersion values in the patient group were found to be statistically significantly higher compared to the control group ($p=0.009$; $p<0.001$, respectively). Tp-e interval was statistically significantly higher in the patient group compared to the control group ($p<0.001$). In the patient group, the Tp-e/QT ratio and the Tp-e/QTc ratio were statistically significantly higher than in the control group ($p<0.001$; $p<0.001$, respectively). In our study, no statistically significant difference was found in the heart rate in the patient group compared to the control group ($p=0.118$). No significant difference was found between the patient and control groups in terms of P wave, PR interval, QRS complex and QT interval values.

In a study in which vitamin B12 and echocardiographic markers were evaluated in 367 patients who underwent angiography, a significantly decreased left ventricular EF was found in the B12 deficient group (9). In our study, LVEDD, LVESD, end-diastolic IVSd, end-diastolic LVPWd, EF and SF measurements were made in the patient and control groups as classical echocardiography measurements. No significant difference was not found in the EF and SF values in both groups. The mean IVSd and LVPWd values of the patient group were statistically significantly higher compared to the control group ($p=0.013$ and $p=0.040$, respectively).

A statistically significant negative correlation was found between the level of vitamin B12 and age in all cases included in the study ($r=-0.175$). It is known that atherosclerosis resulting from endothelial dysfunction starts in childhood (6). The correlation between age and ECG parameters was evaluated in all cases. Any statistically significant correlation was not found between age and Tp-e interval, Tp-e/QT, Tp-e/QTc values.

Study Limitations

The sample size of the study is small. Our study is not planned for long term and thus, it does not provide the opportunity to evaluate the clinical findings of ECG changes in the future. Possible changes in the post-treatment ECG findings of the vitamin B12 deficient group could not be assessed due to time restrictions. However, our study is important for revealing the effect of isolated vitamin B12 deficiency on the electrical activity of the heart in order to eliminate the effect of other vitamin values on ECG findings, considering that iron deficiency and vitamin D deficiency and ECG changes were examined in previous studies.

Conclusion

In conclusion, our study provides significant findings to detect early signs of cardiovascular events that may occur in the childhood age group with vitamin B12 deficiency. Repolarization differences compared to the normal population may reflect early subclinical findings associated with Vitamin B12 deficiency. Further prospective studies with larger samples are needed to identify these early period changes and their clinical significance.

Authorship Contributions

Concept: C.Y., N.S., Design: C.S., M.E., Data Collection or Processing: N.S., C.Y., Analysis or Interpretation: C.Y., K.S., M.E., Literature Search: C.Y., N.S., Writing: C.Y., K.S., M.E., N.S.

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Effect of Subcutaneous Immunotherapy on The Natural Course of Allergic Diseases in Pediatric Patients: A Real-Life Cohort

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Abstract

Aim: Specific allergen immunotherapy (SIT) is the only disease-modifying therapy for allergic diseases. We aimed to examine the effect of subcutaneous specific allergen immunotherapy (SCIT) applications on the prognosis of asthma and allergic rhinitis in pediatric cases in real-life settings.

Methods: The study was designed as a retrospective cohort study. Patients with asthma and/or allergic rhinitis aged between 5 and 18 years old were enrolled between 2010 and 2015. The groups who received SCIT and who did not receive were compared in terms of disease severity parameters in follow-up recorded in their files.

Results: A total of 298 cases, among which 140 received subcutaneous specific allergen immunotherapy. The frequency of asthma, allergic rhinitis, and co-morbidity was similar between the two groups. In the first year of the follow-up, asthma symptoms severity was not significant between the two groups; however, both asthma and allergic rhinitis symptoms were significantly lower in the SCIT patients at the end of the third year of follow-up. While the follow-up rate for three years or more was 62% in the group that received subcutaneous specific allergen immunotherapy, it was 38% in the group that did not receive.

Conclusion: These results showed that SIT is an effective treatment modality in real-life settings with low side effects in pediatric patients with uncontrolled asthma and allergic rhinitis despite medical treatment.

Keywords: Child, subcutaneous, immunotherapy, asthma, allergic rhinitis

Introduction

With the administration of allergen extracts, specific allergen immunotherapy (SIT) is the only disease-modifying therapy for allergic diseases that results in the development of allergen-specific blocking antibodies and tolerance-inducing cells (1). Subcutaneous specific allergen immunotherapy (SCIT), alleviates the symptoms of allergic diseases such as asthma and allergic rhinitis with or without conjunctivitis (AR) and prevents the onset of new allergen sensitivities (2,3). Most importantly, clinical efficacy persists for many years after SCIT is over.

However, the duration for SCIT is three to five years to provide optimal disease control with a possible long-term effect (4). Although randomized controlled trials have shown the efficacy and safety of SCIT in pediatric cases with asthma and AR, real-life results may not be as successful considering the dropouts and non-adherence. Moreover, the natural course of allergic diseases tend to change in years; thus, it is essential to compare the prognosis in children who receive SCIT and those who do not in real-life settings.

In this retrospective cohort study, we aimed to compare the prognosis of allergic asthma and AR in pediatric cases who receive SCIT and not in real-life settings.

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Methods

Research Method

This is a retrospective cohort study approved by the Celal Bayar University Faculty of Medicine Institutional review board (6.6.12/193). In our retrospective cohort study, patient files were scanned with the ethics committee's approval; the consent form was not obtained from the patients.

Study Population

Patients with asthma or AR, aged between five and eighteen, presented to our clinic between 2010 and 2015, and were diagnosed with allergen sensitization by skin prick test (SPT) were enrolled in the study. The groups who received SCIT and who did not receive SCIT were compared in terms of disease severity parameters in follow-up recorded in their files.

Asthma was diagnosed according to GINA guidelines with recurrent bronchial obstruction findings and reversibility with an inhaled bronchodilator, while AR was diagnosed according to ARIA guidelines with recurrent sneezing, nasal drainage, nasal itching, and nasal obstruction and/or conjunctival findings (5,6).

Data Collection

SPT results performed in our clinic between 2010 and 2015 were obtained from computer records, and the ones that were found to be positive were selected. Files of these selected patients were reviewed for age, sex, diagnosis, family history of allergies, number of siblings, and, if any, accompanying allergic diseases. Moreover, information about treatment onset, duration, side effects were recorded for the ones who received SCIT, and the reason for not starting SCIT was recorded from the files for the ones who did not.

In AR cases, clinical severity was recorded as intermittent/persistent and mild-moderate-severe according to ARIA classification during the first and third years of follow-up.

In asthma cases, the number of emergency asthma visits, in-hospital days for asthma exacerbations, number of days of systemic steroid treatment, and the number of asthma exacerbations were recorded for the first and third years of SCIT treatment.

Allergen Prick Test

Skin prick tests were performed (Allergopharma, Germany) with Dermatophagoides Farinae, Dermatophagoides Pteron, Alternaria Tenius, Cat Ephitel, Olive Tree, Plantago Lanceolata, Grasses Mix, Küchenschabe. A positive control (histamine 10 mg/mL Allergopharma, Germany) in duplicate and a negative (saline) control according to EAACI guidelines (7).

Immunotherapy

SCIT was given in a clinic setting and included a 12-week induction period. The maintenance dose was the highest tolerated dose reached during the induction process, and it was repeated every 28th day for a total of 3-4 years. Allergen extracts from Allergopharma (Joachim Ganzer KG, Reinbek, Germany) were used for specific subcutan immunotherapy. Active treatment involved a standardized D. Pteronyssinus (50%) and D. farinae, standardized Alternaria Alternata extracts (100%), standardized Allergovit 6-grasses, a 100% mixture of allergens from 6 grass pollen species (*Holcus lanatus, Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis, and Festuca pratensis*), and standardized Oliea Europaea (100%) extract for specific subcutan immunotherapy.

Statistical Analysis

Data analysis was performed using SPSS version 22.0 (IBM Corp, Armonk, NY, US). Statistical analysis included descriptive statistics, Student's t-test, Pearson chi-square tests, paired sample t-test, and Mann-Whitney U analysis. Group comparisons were performed using the Student's t-test for continuous variables and χ^2 test to compare categorical variables. Categorical variables were reported as frequency and percentage. Paired sample t-test was used to assess the difference between first-year and third-year changes. Mann-Whitney U analysis was used to compare continuous variables not normally distributed between SCIT (+) and SCIT (-) groups. A p-value less than 0.05 was considered statistically significant.

Results

Sociodemographic Characteristics of the Study Population

A total of 298 cases were enrolled; among which 140 received SCIT (64% male) while 158 patients did not receive SCIT for various reasons (63% male) (p=0.86).

Mean age at admission was higher in the SCIT group compared to the non-SCIT groups (9.9-3.2 vs. 8.8-3.8 years, p=0.01). Other characteristics such as the presence of sibling and familial history of allergy were not significantly different between the groups (p=0.23, p=0.44 respectively) (Table 1).

Clinical Characteristics of the Study Groups

Among the 298 subjects enrolled in this study, 114 had asthma, 157 had AR, 27 had asthma and AR, while 52 had other additional allergic diseases. The frequency of asthma, AR, and other allergic diseases was not significantly different between the SCIT and non-SCIT groups (p=0.35, p=0.36 respectively) (Table 1).

The number of inhaled bronchodilator use, asthma-related emergency visits, days of systemic steroid use, and

in-hospital days for asthma were not significantly different between the two groups (p=0.07, p=0.14, p=0.49, p=0.53, respectively). In contrast, the number of asthma exacerbations was significantly higher in the group who received SCIT (2.7±1.6 vs. 2.0±1.1 p=0.03) (Table 2).

Among the total of 184 AR cases, the frequency of intermittent AR was not significantly different between the ones that received SCIT and did not receive SCIT (63% and 72% respectively, p=0.27). On the other hand, among the ones who received SCIT frequency of severe AR at the baseline was significantly higher (10% and 0% respectively, p=<0.001) (Table 2).

Sensitization patterns were not significantly different between the subjects who received SCIT and not (p=0.58). Both in the SCIT and non-SCIT groups, the most common allergen sensitized to was grass and tree pollens (45% and 53% respectively), followed by dermatophagoid (14% and 12% respectively). The frequency of sensitization to more than two allergens was 20% in the SCIT group and 17% in the non-SCIT group.

Table 1. Demographic characteristics and clinical findings of the cases

	With SCIT (n=140)	Without SCIT (n=158)	p
Boys*	90 (64)	100 (63)	0.86***
Age (years)***	9.9±3.2	8.8±3.8	0.01**
Family allergic disease*	96 (69)	103 (65)	0.54***
Sibling presence*	82 (59)	80 (52)	0.23***
Indication of immunotherapy			
Asthma*	51 (36)	63 (40)	0.35***
AR*	79 (56)	78 (49)	
Asthma + AR*	10 (8)	17 (11)	
Additional allergic disease			
Urtikeria*	24 (17)	21 (13)	0.36***
Atopic dermatitis*	1 (1)	4 (3)	
Urtikeria + Atopic dermatitis*	1 (1)	1 (1)	

*Expressed as n (% of the SCIT group)
**Student's t-test
***Chi-square test
There were no significant differences between the two groups in terms of demographic characteristics and clinical findings. SCIT: Subcutaneous specific allergen immunotherapy, AR: Allergic rhinitis

Treatment and Follow-up

Among the cases who did not undergo SCIT, the most common reason was the family's rejection of treatment in 133 (72%) and doctor's decision in 44 (24%) cases.

It was found that 56 subjects did not complete the SCIT, and the reason was mainly economic (n=55) while one had an extensive local reaction.

Among the 140 subjects in the SCIT group, 53 subjects (38%) were lost to follow-up at the end of three years,

Table 2. Initial clinical characteristics of with SCIT and without SCIT groups

Asthmatic cases	With SCIT n=61	Without SCIT n=80	p
Age at onset of asthma (years)*	5.3 (3.5)	3.9 (2.8)	0.03**
Onset of AR (years)*	4.6 (3.1)	4.7 (4.1)	0.79**
Asthma exacerbations (per year)*	2.7 (1.6)	2.0 (1.1)	0.03**
Inhaled bronchodilator use (dose/day/exacerbations)	11.0 (7.1)	8.6 (5.2)	0.07***
Emergency admissions (days/year)*	1.3 (1.8)	0.8 (1.3)	0.14***
Systemic steroid use (days/year)*	1.2 (1.4)	1.1 (1.5)	0.49***
In hospitalization for asthma (days/year)*	0.3 (1.2)	0.5 (1.5)	0.53***
Allergic rhinitis cases	With SCIT n=89	Without SCIT n=95	p
Distribution of allergic rhinitis			
Intermittent****	56 (63)	68 (72)	0.27*****
Persistent****	33 (37)	27 (28)	
Allergic rhinitis severity			
Mild****	25 (28)	52 (56)	<0.001*****
Moderate****	55 (62)	43 (43)	
Severe****	9 (10)	0 (0)	

*Expressed as mean (standard deviation)
**Student's t-test
***Mann-Whitney U test
****Expressed as n (% of the group)
*****Chi-square test
While there was no significant difference between the initial asthma findings with between with SCIT and without SCIT Groups, allergic rhinitis's clinical features were more severe in cases in whom SCIT was initiated.
SCIT: Subcutaneous specific allergen immunotherapy, AR: Allergic rhinitis

while the loss to follow-up rate was higher among the 158 subjects in the non-SCIT group with 62%. Among the SCIT (+) and (-) group followed up for three years, 9 and 6 subjects had asthma and AR, respectively.

At baseline, the severity classificant of AR subjects who received SCIT was 28% mild, 62% moderate, and 10% was severe, while these severity parameters changed significantly as 80% mild and 20% moderate (p<0.001) (Table 3).

Disease severity parameters did not change significantly at the end of three years in the group that did not receive SCIT. On the other hand, in the group that received SCIT, all asthma severity parameters decreased significantly during the third year of follow-up compared to the first year (Table 4).

Among the SCIT (+) and (-) group followed up for three years, 9 and 7 subjects had asthma and AR comorbidity, respectively.

Discussion

The results of this study indicate that in real-life conditions, SCIT significantly decreases the severity of AR and improves asthma control in children. The major obstacle in treatment adherence seems to be an economic burden.

SCIT is the only disease-modifying treatment strategy for IgE-mediated allergic diseases in children and adults (8). It reduces symptoms in pediatric subjects with AR and asthma while increasing allergen-specific immune tolerance in the long term (9-11). However, although it has severe effects on symptom relief in asthma and AR, it remains a secondary treatment for symptomatic drugs because of the cost, length of treatment, the need for serious patient compliance, and concerns about safety and individual efficacy (12). Similarly, our results demonstrated that socioeconomic conditions were the most common reason for not starting SCIT and for early termination.

In our study, AR was the most common indication for SCIT initiation. AR is one of the most common allergic diseases and is classified as mild, moderate, or severe and as intermittent or persistent (13,14). In our study, the majority of subjects that received SCIT were intermittent with moderate severity, whereas the majority of cases that did not receive SCIT were intermittent with mild severity. The aim of treatment in AR is to control symptoms and reduce inflammation. AR treatment consists of intranasal

Table 3. First and third year distribution and severity of AR in cases with/without SCIT

Allergic rhinitis cases		With SCIT			Without SCIT		
		1. year n=89	3. year n=64	p	1. year n=95	3. year n=38	p
AR severity	Mild (%)*	25 (28)	51 (80)	0.001**	52 (56)	15 (40)	0.10**
	Moderate (%)*	55 (62)	13 (20)		43 (44)	22 (57)	
	Severe (%)*	9 (10)	0		0	1 (3)	
AR distribution	Intermittent (%)*	56 (63)	62 (97)	0.001**	68 (72)	31 (82)	0.23**
	Persistent (%)*	33 (37)	2 (3)		27 (28)	7 (18)	

***Expressed as n (% of the SCIT group)**
****Chi-square test**
While the distribution and severity of AR in the cases who underwent SCIT decreased significantly in the third year compared to the baseline, there was no significant change in the group without SCIT.
SCIT: Subcutaneous specific allergen immunotherapy, AR: Allergic rhinitis

Table 4. First and third year asthma characteristics in cases with/without SCIT

Ashmatic	With SCIT			Without SCIT		
	1. year n=61	3. year n=32	p	1. year n=80	3. year n=28	p
Inhaled bronchodilator used (days/year)*	11.0 (7.2)	3.4 (3.3)	<0.001**	8.6 (5.3)	5.8 (5.9)	0.08**
Emergency admissions (days/year)*	1.3 (1.8)	0.1 (0.2)	0.001**	0.8 (1.3)	0.3 (0.8)	0.18**
Systemic steroid use (days/year)*	1.2 (1.4)	0.3 (0.7)	0.001**	1.1 (1.5)	0.6 (0.8)	0.43**
In hospitalization for asthma (days/year)*	0.3 (1.2)	0	0.16**	0.5 (1.5)	0.1 (0.3)	0.57**
Asthma exacerbations (per year)*	2.7 (1.7)	0.7 (1.8)	<0.001**	2.0 (1.2)	(1.6)	0.26 **

*Expressed as mean (standard deviation)
**Paired samples t-test
While the clinical features of asthma decreased significantly in the third year compared to the baseline in patients who underwent SCIT, there was no statistically significant change in the without SCIT group.
SCIT: Subcutaneous specific allergen immunotherapy

steroids, oral-intranasal antihistamines, and leukotriene receptor blockers; however, with these treatments, the natural course of the disease does not change, and in some patients, the symptoms persist despite treatment (13,15). SCIT administration with susceptible allergens not only desensitizes the patient but also provides long-term clinical improvement that can persist even years after treatment (15,16).

The clinical efficacy of SCIT was determined for both AR and asthma (17,18). Previous studies have also reported that SCIT significantly reduces both rhinitis and asthma-related symptoms and drug scores from the first year of treatment (19). As an addition to these studies, we had a group that was tested but did not start treatment giving us the opportunity to observe the natural course of disease in time. And we observed that AR distribution and AR severity were significantly improved in the SCIT group, similar to previous research, and the non-SCIT group did not change significantly in time.

Asthma is one of the most common chronic inflammatory respiratory diseases of childhood, and remodeling in the airway can cause asthma to continue in adulthood (20). Pharmacological drugs used for asthma can effectively treat asthma symptoms and the inflammatory process associated with asthma, but the symptoms may recur when the medication is discontinued (20). SCIT is the only treatment modality that can alter the natural course of allergy and prevent new sensitivities and clinically worsening symptoms (21). SCIT decreases asthma symptoms, the need for rescue medication, and the frequency of asthma attacks and increases the quality of life (22,23). From the Cochrane Database meta-analysis for SCIT, both dermatophagoid and pollen immunotherapy were found to be effective in symptom scores in asthmatics and reported that pollen immunotherapy had better outcomes than mite immunotherapy (24). In another meta-analysis, it was reported that the use of asthma control medication after SCIT was moderately intense, reducing the use of medications for asthma (25). Consistent with these data, in our study, it was observed that SCIT treatment significantly reduced the need for salbutamol in SCIT treatment, emergency admission, and asthma attacks. There was no significant change in asthma control markers except the need for inhaled bronchodilators in the group who did not receive SCIT and started medical treatment.

There was no difference between the clinical course of SCIT treated monoallergen and poly-allergen susceptibility cases in our study group. In the literature, as a result of the studies on the effectiveness of immunotherapy in cases with polysensitized and monosensitized susceptibility, it has been concluded that allergens can be clinically effective if adequately identified and treated with these allergens insufficient time and inadequate doses (26). Our study concluded that the proper selection of the allergens to be applied in immunotherapy and the initiation of immunotherapy in patients with polyallergenic sensitivity is effective in the treatment.

SCIT induced reactions are generally divided into two groups as local and systemic reactions. The local reaction may include pruritus, erythema, and swelling at the injection site, and the systemic reaction may range from a mild reaction to a very severe life-threatening anaphylaxis (27). The American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology reported in the surveillance report of SCIT that the overall Systemic Reaction rate was 0.1% (28); we did not have any systemic reactions in our cohort. Local reactions have been reported between 0% and 50% (25,29,30). In our study, edema and hyperemia of 4 cm in diameter were observed in 7 (3.5%) patients, while the larger local reaction was observed in only 1 (0.5%) case in the SCIT group.

The strong point of our study is the retrospective cohort design allowing us to see real-life data. Moreover, follow-up evaluation of a group that was tested during the same time period but did not receive SCIT allowed us to observe the natural course of the disease and compare SCIT effects with the natural course.

Study Limitations

The major limitation of our study was the loss of follow-up. Especially, regular follow-up of the patients not receiving SCIT was lower than those in the group receiving SCIT. Not receiving SCIT cases may be out of follow-up because their clinical symptoms have improved over the years.

Conclusion

SCIT is an effective and safe treatment modality in pediatric AR and asthma subjects modifying the natural course of the allergic disease and medical treatment requirements. The economic burden of treatment is the major non-adherence reason and needs to be addressed at the beginning of treatment.

Authorship Contributions

Concept: O.Y., A.Y., H.Y., Design: O.Y., H.Y., Data Collection or Processing: Y.S., S.A., B.K., Analysis or Interpretation: O.Y., A.Y., Literature Search: O.Y., A.Y., H.Y., Y.S., Writing: A.Y. S.A., B.K.

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Original Article

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The Assessment of Thyroid Hormone Levels in Term and Preterm Infants Diagnosed with Transient Tachypnea of the Newborn: A Cross-Sectional Study

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Abstract

Aim: The study aims to evaluate the effect of thyroid hormone levels on the development of transient tachypnea of the newborn (TTN) and neonatal outcomes in preterm and term infants during hospitalization.

Methods: Eighty-seven newborns with gestational age ≥34 weeks admitted to neonatal intensive care unit (NICU) between January 2016 and December 2019 were enrolled in our retrospective study. The hospital database system and patient files were scanned for data collection. Infants were divided into three groups (late preterm, early term, and term). Maternal features and demographic characteristics, thyroid hormones, neonatal outcomes during hospitalization of newborns with TTN were recorded.

Results: The mean fT4 level was 1.51±0.33 ng/dL and the median thyroid-stimulating hormone (TSH) level was 3.1 mIU/L. Among 87 infants, 21 were late-preterm, 41 were early-term, and 25 were term infants. There was no difference in the mode of delivery, gender, need, and duration of mechanical ventilation, and non-invasive ventilation or O_2 therapy. The mean fT4 level was 1.35±0.29 ng/dL in late preterms 2.5±2.1 ng/dL in early terms and 1.56±0.25 ng/dL in term infants. Late preterms had a lower fT4 level than early term and term groups which was statistically significant but no difference was present between subgroups in TSH levels.

Conclusion: Evaluation of thyroid function should be considered especially in preterm babies hospitalized to NICU because of respiratory distress for an individualized approach if treatment is needed.

Keywords: Newborn, thyroid hormones, transient tachypnea of newborn

Introduction

Transient tachypnea of the newborn (TTN) is described as a benign, respiratory condition mostly in late preterm and term newborns. Even though TTN is a self-limiting and spontaneously resolves within 48-72 hours in the majority, occasionally there is a need for hospitalization in the neonatal intensive care unit (NICU) and may cause morbidities like hypoxemia, pulmonary air leak syndrome, persistent pulmonary hypertension, and mortality (1-3).

The main underlying pathology is delayed reabsorption of lung alveolar fluid and failure of the lung to expand which is crucial for the transition from placental to pulmonary gas exchange (4). During the postnatal respiratory adaptation, alveolar epithelial cells take place in the transport of active solutes creating osmotic gradients results in alveolar fluid clearance (5). Na+/K+-ATPase and epithelial Na channels play a major role during this process (6). At birth, amiloride-sensitive sodium is transported via passive movement from the lumen to the alveolar epithelial cells through and sodium is extruded from the cell across the basolateral membrane to the interstitium by Na+/K+-ATPase. By those movements, an osmotic gradient is generated and pulmonary fluid passively passes through the intercellular space (7-9). Hormones like glucocorticoids, thyroid hormones, and catecholamines have a regulatory effect during the activity of sodium absorption which happens just before or in the course of delivery (6). Hypothyroidism has an inhibitory effect on fetal lung fluid resorption in utero (10). Preterm newborns have low levels of both total and free thyroxin which rise by gestational week and are found in higher levels than

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fetal concentrations after postnatal 4 to 5 days with the surge of thyroid-stimulating hormone (TSH) (11,12).

Although risk factors for TTN are well established in the literature, there is limited knowledge about the effect of thyroid hormones on the development of TTN in preterm and term infants. Several studies are reporting the fT4 and TSH levels in preterm and term infants with TTN but there is limited information about neonatal outcome during hospitalization. So we aimed to evaluate thyroid functions related to neonatal outcomes among term and preterm newborns diagnosed with TTN who were admitted to our NICU (11,13-16).

Methods

Study Design

Newborns with gestational weeks (GW) above 33 weeks who were hospitalized to our NICU between January 2016 and December 2019 were enrolled in our retrospective study. A total number of 4450 newborns were born in our hospital during this study period and 618 babies were admitted to our NICU. Among these babies, 106 infants were diagnosed with TTN, 19 of them were excluded because of incomplete data for thyroid hormones and finally, 87 infants were included in the study. These 87 infants were divided into three subgroups and comparatively analyzed (late preterm-n; 21, early term-n; 41 and term-n; 25) (Figure 1) Hospital database system and patient files were scanned for data collection and data on maternal features such as maternal age, parity, birth weight, gender, GW, the mode of delivery, Apgar scores (1st and 5th minute), need of oxygen or mechanical ventilation support, length of hospital stay, mortality and fT4 and TSH levels were recorded. Congenital metabolic disorders, pneumothorax, early-onset sepsis, hypoxic ischemic encephalopathy, major congenital anomalies, and congenital hypothyroidism or received thyroid hormone therapy were our major exclusion criteria.

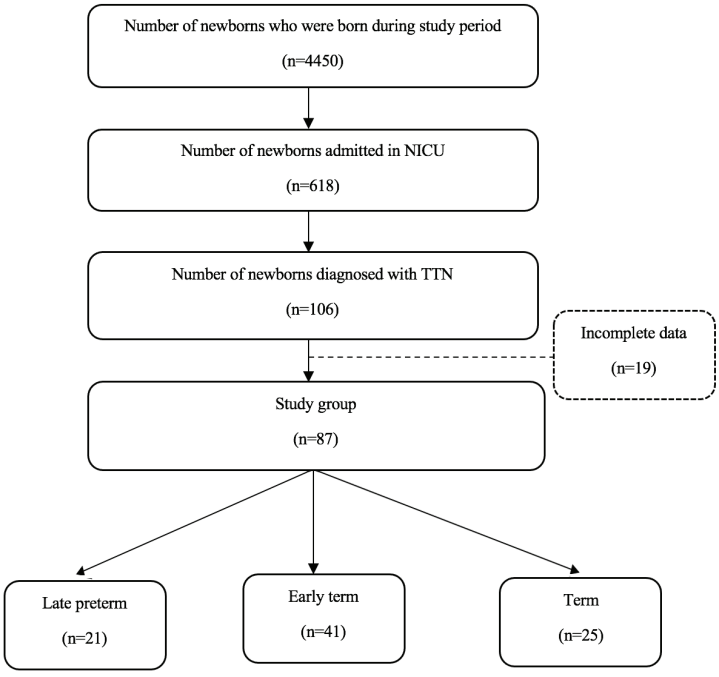

Figure 1. Flow diagram of the study
NICU: Neonatal intensive care unit, TTN: Transient tachypnea of the newborn

All procedures performed in studies involving human participants 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. This article does not contain any studies with animals performed by any of the authors. Ethical clearance was obtained from the Ethics Committee of Haseki Training and Research Hospital date and report number: 08.07.2020 - 2020-143.

Neonatal Features

Three subgroups were determined for newborns in accordance with the GW. Late-preterm newborns included babies who were born between 34 to 36+6 weeks, early-term newborns included babies from 37 to 38+6 weeks and term newborns from 39 to 41+6 weeks. GW was determined according to the beginning of the mother's last menstrual period or first-trimester ultrasonography. TTN diagnosis was established according to both clinical and laboratory criteria: 1) presence of tachypnea (respiratory rate >60 breaths/min, retractions, nasal flaring, grunting, cyanosis) for minimum of 12 hours, 2) supplemental oxygen support for minimum of 6 hours, 3) radiological findings of TTN (increased central vascular structures, widened interlobar fissure, increased in both hemithorax and flattened diaphragmatic domes, 4) exclusion of pulmonary problems (respiratory distress syndrome, meconium aspiration, congenital pneumonia or heart disease, and other conditions leading to tachypnea such as hypoglycemia, hypocalcemia, polycythemia), in newborns who admitted to NICU (2).

Blood samples were routinely taken for fT4 and TSH levels via venipuncture within postnatal 72 hours in our unit for the newborn metabolic and endocrine disease screening program. Electrochemiluminescence immunoassay system was used to measure levels of fT4 and TSH. TSH reference range was 0.38-5.33 mIU/L and fT4 reference range was 0.61-1.12 ng/dL.

Statistical Analysis

Results were analyzed with SPSS (Statistical Package for the Social Sciences, version 20 software) statistical program. The descriptive statistics are described with

mean ± standard deviation for normally distributed variables and median values (25^{th}-75^{th} percentile) for non-homogeneously distributed variables, and as a frequency (percentage) for categorical variables. The conformity of variables to normal distribution was assessed using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). For multiple group comparisons of categorical variables, the chi-square test was used when the chi-square condition was met and Fisher's exact test was used when the chi-square condition was not met. In multiple group comparisons of numerical variables, the analysis of variance (ANOVA) test was used for normally distributed numerical variables, and the Kruskal-Wallis test was used for non-normally distributed numerical variables. In the post-hoc analysis, the Mann-Whitney U test with Bonferroni correction was used for sub-group analysis of non-normally distributed variables, and the chi-square test with Bonferroni correction was used for sub-group analysis of categorical variables. Statistical significance was considered as $p<0.05$.

Results

The mean GA of all infants was 37.5±1.5 weeks and the mean birth weight was 3041±507 g. The mean fT4 level was 1.51±0.33 ng/dL and the median TSH level was 3.1 [interquartile range (IQR) 1.8 to 4.7] mIU/L. Demographic characteristics, maternal features, and neonatal outcomes of all infants and comparison of three subgroups are given in the Table 1.

Among 87 infants, 21 (24.1%) of them were late-preterm, 41 (47.1%) of them were early-term, and 25 (28.7%) of them were term infants. The mean gestational week and birth weight of late preterm, early term, and term newborns were respectively 35.4±0.6 weeks, 37.5±0.5 weeks, 39.4±0.7 weeks and 2631±288 g, 3081±521 g, 3320±410 g. There were statistically significant differences in birth weight of the groups when subgroup analysis was performed according to the gestational week and the gestational week was significantly different between late preterm and early term group. Neither mode of delivery nor male gender was significantly different between the three subgroups. No significant difference was found for mechanical ventilation support and duration and non-invasive ventilation or O_2 therapy. The mean fT4 level was 1.35±0.29 ng/dL in late preterm infants, 2.5±2.1 ng/dL in early term infants, and 1.56±0.25 ng/dL in term infants. Late preterm newborns had a low fT4 level compared to the other groups with a statistically significant difference. The median TSH level was 2.98 mIU/L (2.22 to 3.92) in preterm group, 3.29 mIU/L (1.88 to 5.85) in the term term infants and 3.24 mIU/L (1.57 to 4.87) in term group. No significant difference was found for TSH levels in subgroups. TSH and fT4 levels of all groups and subgroups were given in the Table 2.

The median hospitalization duration was 9 days (IQR) 7 to 14.5 for preterm infants, 8 days (IQR 6 to 10) for early term infants, and 8 days (IQR 5 to 10). No significant difference was found for hospitalization duration among the groups. No patient died in both three groups.

Discussion

We evaluated the thyroid hormone levels in total number of 87 late preterm and term diagnosed with TTN. Our study demonstrated that fT4 levels were significantly lower in late preterms compared with early-term and term newborns. During postnatal adaptation, fT4 and total T4 levels have low levels and as TSH has a rise within 4-5 days after birth, concentrations of T4 begin to increase which is directly proportional to gestational age of the newborn (12). Late preterm babies have physiological immaturation so they tend to have more respiratory adaptation problems that sometimes result in TTN as a consequence of delayed transition from fetal life during the postnatal period (13,17). Late preterm infants do not have mature hypothalamic-pituitary-thyroid axis which is assumed as a robust factor to adapt to life after birth (18). This information supports our major finding in the study that lower fT4 values were detected in late-preterm babies, similar levels between early term and term newborns. In the literature, some studies reported similar results as in our study. Kayıran et al. (14) evaluated thyroid hormone levels in newborns with TTN, categorized by GW and compared with healthy newborns. They reported that fT4 levels of the newborns with TTN were significantly lower in late-preterms than healthy babies and early-term and term neonates with TTN had higher TSH levels (14). Atasay et al. (15) also studied cord blood TSH, free T3 (fT3), fT4, cortisol, epinephrine, and adrenocorticotropic hormone in the newborns having TTN and compared to the healthy group. There was no significant difference for both fT4 and TSH levels was significantly different but newborns having TTN had significantly lower fT3 levels. No significant difference was found between groups for TSH levels in our study and fT3 levels could not be evaluated since the study was designed as retrospective.

Several previous studies reported the relation between thyroid hormones and respiratory diseases. The study of Paul et al. (19) showed that there was an important relationship between low fT4 and severity of disease after birth. Low fT4 levels were found to be related to increased respiratory disease in late preterm babies (19). We found no significant difference in respiratory morbidities among late preterm and term infants. Lim et al. (20) evaluated thyroid function including total T4 and

TSH but not the bioavailable form as fT4 in term infants who were mechanically ventilated in their retrospective study. Biswas et al. (16) reported lower levels of fT4 in mechanically ventilated preterm infants who were born <30 GW. Vanhole et al. (21) also found that low thyroid hormone levels were related with worse neonatal outcomes. Although late preterm infants have lower fT4 levels than term infants, we did not find any difference in need and duration of invasive or non-invasive mechanical ventilation, hospital stay, and death among late preterm and term newborns.

In several studies as cesarian section is found as one of the leading risk factors for the development of TTN (22-24). There was no significant difference in the mode of delivery between groups in our study and cesarian section was not found related to the development of TTN similar to the studies of Kayıran et al. (14) and Zanardo et al. (25). Same findings were available for the relation between male gender and TTN among groups. There was no difference in gender for late preterm and term infants.

Table 1. Demographic characteristics and neonatal outcomes of the newborns

Characteristic		All patients (n=87)	Late preterm (n=21)	Early term (n=41)	Term (n=25)	p
Demographic information						
Maternal age (years), mean ± SD		28.0±6.9	26.8±6.3	28.5±7.3	28.2±6.6	0.750
Gravida, median (IQR 25-75)		2 (1 to 3)	2 (2-3)	2 (1 to 3)	2 (1 to 3)	0.619
Mode of delivery, n/N (%)	C/S	54/87 (62.1)	11/21 (52.4)	29/41 (70.7)	14/25 (56)	0.286
Gender, n/N (%)	Male	54/87 (62.1)	13/21 (61.9)	25/41 (61)	16/25 (64)	0.970
Gestational age (week), mean ± SD	-	37.5±1.5	35.4±0.6	37.5±0.5	39.4±0.7	<0.001[a, b]
Birth weight (g), mean ± SD	-	3041±507	2631±288	3081±521	3320±410	<0.001[a, b, c]
Cord blood gases	pH, median (IQR 25-75)	7.31 (7.28 to 7.35)	7.3 (7.28 to 7.34)	7.31 (7.28 to 7.35)	7.31 (7.25-7.34)	0.756
	Base excess, median (IQR 25-75)	-3.1 (-6.3 to -1.5)	-3.1 (-5.1 to -1.0)	-3.0 (-6.4 to -1.7)	-3.40 (-7.0 to -1.6)	0.848
	Bicarbonate, mean ± SD	20.2±3.3	20.4±0.7	20.1±2.9	20.1±3.8	0.562
	Lactate, mean ± SD	2.1±1.6	1.5±1.3	2.07±1.4	2.6±1.9	0.162
APGAR scores	1st-minute, median (IQR 25-75)	8 (7 to 9)	8 (7 to 9)	8 (7 to 9)	8 (6 to 9)	0.509
	5th-minute, median (IQR 25-75)	9 (9 to 10)	9 (9 to 10)	9 (9 to 10)	9 (8.5 to 10)	0.773
Respiratory status	Need of MV, n/N (%)	8/87 (9.2)	3/21 (14.3)	2 /41 (4.9)	3/25 (12)	0.410
	Duration of MV, mean ± SD	2.3±2.1	1.33±0.57	2.5±2.1	3.3±3.2	0.607
	Need of NIMV, n/N (%)	40/87 (46)	14/21 (66.7)	15/41 (36.6)	11/25 (44)	0.08
	Duration of NIMV, median (IQR 25-75)	2 (1 to 2)	1.5 (1-3)	2 (1 to 2)	1 (1 to 2)	0.750
	Duration of oxygen therapy, median (IQR 25-75)	2 (1 to 3)	2 (1-3)	2 (1-3)	1 (1-2)	0.448
Outcome, n/N (%)	Length of stay at hospital (days), median (IQR 25-75)	8 (6 to 10)	9 (7 to 14.5)	8 (6 to 10)	8 (5 to 10)	0.137
	Dead, n/N (%)	0/87 (0)	0/21 (0)	0/41 (0)	0/25 (0)	1

[a]Different from Late Preterm + Early Term; [b]Different from Late Preterm + Term group; [c]Different from Early Term + Term
IQR: Interquertile range, C/S: Cesarian section, MV: Mechanical ventilation, NIMV: Non invasive mechanical ventilation, IQR: İnterquartile range, SD: Standart deviation

Table 2. Thyroid hormone levels of the newborns

Hormone levels	All patients (n=87)	Late preterm (n=21)	Early term (n=41)	Term (n=25)	p
fT4 (ng/dL), mean ± SD	1.51±0.33	1.35±0.29	2.5±2.1	1.56±0.25	0.024[a, b]
TSH, (mIU/L), median (IQR 25-75)	3.1 (1.8 to 4.7)	2.98 (2.22 to 3.92)	3.29 (1.88 -5.85)	3.24 (1.57 to 4.87)	0.678

[a]Different from Late Preterm + Early Term, [b]Different from Late Preterm + Term group
fT4: Free Thyroxin 4, TSH: Thyroid stimulating hormone, SD: Standart deviation, IQR: İnterquartile range

Study Limitations

This study has some limitations. Our study was a single-center study representing a small number of infants. We could not compare with healthy infants since it was designed as retrospective. Further prospective studies with a larger number of infants are needed to make a clear interpretation of the effect of thyroid hormones on respiratory diseases, especially in infants.

Conclusion

Preterm newborns had different thyroid hormones basically due to gestational age compared to term newborns diagnosed with TTN in our study. Evaluation of thyroid function should be considered especially in preterm newborns who were hospitalized to the NICU because of respiratory problems for an individualized approach if treatment is needed.

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Authorship Contributions

Concept: E.A., B.C., Design: E.A., B.C., Data Collection or Processing: E.A., B.C., Analysis or Interpretation: B.C., D.O., D.K., D.B., Literature Search: E.A., D.O., D.K., D.B., Writing: B.C.

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

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Original Article

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Prognostic Factors of Operated Stage I Non-Small Cell Lung Cancers: A Tertiary Center Long-Term Outcomes

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Abstract

Aim: This study aimed to evaluate prognostic factors influencing survival in patients who underwent surgical resection of stage I non-small cell lung cancer (NSCLC) in our center.

Methods: A total of 472 patients with stage I NSCLC who were operated between January 2007 and November 2018 were retrospectively analyzed in the study. Patient data was collected using hospital database. The remaining patients were divided into 2 groups: patients younger than 65 years of age (group A) and those aged 65 and over (group B).

Results: The patient group comprised 80 women (16.9%) and 392 men (83.1%); 152 patients were aged 65 years or over (32.2%) and 320 patients were under 65 years of age (81.5%). The mean follow-up time was 51 months. The 5-year survival rate was 67.2% overall. Patients with stage IA1, IA2, IA3, and IB tumors had 5-year survival of 78.1%, 72.5%, 77.3%, and 56.7%, respectively (p=0.009). In multivariate analysis, advanced age (≥65 years), large cell carcinoma, left-sided surgery, and higher tumor stage were the most important prognostic factors associated with poorer survival.

Conclusion: Advanced age was determined to be an independent poor prognostic factor, and sub-group analyses showed that survival outcome was better with tumors smaller than 1 cm. Based on the results of our study, we believe that the classification of stage I group should be revised in the new edition of lung cancer staging.

Keywords: Survival rate, carcinoma, non-small-cell lung, prognosis

Introduction

Lung cancer is the most common adult cancer and the leading cause of cancer deaths worldwide and in Turkey. According to the most recent statistics from the Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, the age-standardized incidence rate of lung cancer in Turkey was reported as 57.7 in 100000 men and 9.8 in 100000 women (1). Lung cancer patients over 75 years of age are especially challenging in terms of selecting a treatment protocol and approach. While the standard treatment approach recommended for early (stage I) lung cancer is surgical anatomic resection, older patients with advanced disease undergo surgery less frequently than younger patients (2). Despite reports of higher postoperative complication and mortality rates in this population, careful patient selection, preoperative multidisciplinary evaluation, and postoperative rehabilitation provide more moderate survival rates (3-7).

In the eighth edition of the tumor, node, metastasis (TNM) classification, stage I tumors are divided into 4 groups based on survival rates (stage IA1, IA2, IA3, and IB) (8). In previous studies, survival rates in the stage I sub group have varied depending on factors such as age, sex, and histological cell type. For early-stage tumors in all age groups, the consensus among many researchers is that survival rates with tumors smaller than 2 cm are better compared to the other groups (9-12).

Our aim in this study was to determine the impact of advanced age on survival in patients who underwent surgical resection of early non-small cell lung carcinoma

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(NSCLC) and evaluate the survival outcomes of stage I tumor subgroups.

Methods

Study Design

Data pertaining to patients who underwent surgery due to NSCLC between January 2007 and December 2018 were obtained from a prospective database and analyzed retrospectively. Patients whose data could not be accessed, who underwent sublobar (wedge) resection due to limited respiratory function, functional inoperable patients or were Stage I after neoadjuvant therapy were excluded from the study.

The remaining patients were divided into 2 groups: patients younger than 65 years of age (Group A) and those aged 65 and over (Group B). The ethics committee Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital and Helsinki approval for the study was obtained from the institutional review board (no: 2020-54).

Patient Selection

All patients underwent preoperative thoracic computed tomography (CT) for evaluation of primary disease, as well as positron emission tomography (PET/CT) and cranial magnetic resonance imaging for evaluation of distant metastasis. The pulmonary reserve was assessed by pulmonary function tests. The preoperative mediastinal staging was performed in accordance with the European Society of Thoracic Surgeons (ESTS) guidelines (13).

Postoperative Follow-up

Patient demographic data, mortality, histopathological characteristics, recurrence, and 5-year survival rates were analyzed. Age, histopathology, tumor Stage, and survival data were obtained from hospital records and the national survival database. Pathologic staging was performed according to the 8th edition of the TNM classification system.

Patients were followed up in collaboration with oncologists by physical examination and thoracic CT every 3 months for the first 2 years, every 6 months from years 2 to 5, and once a year thereafter. An oncologist was present during all postoperative examinations.

Statistical Analysis

The patients' demographic and clinical data were evaluated using descriptive statistics. Relationships between categorical data were evaluated using chi-square (χ^2) or Fisher's Exact test. Student's t and Mann-Whitney U tests were used for comparisons of continuous variables. Survival was evaluated using Kaplan-Meier analysis, and log-rank analysis was performed to compare factors. A $p<0.05$ was considered statistically significant. All tests were performed on SPSS version 22 (IBM Corp., Armonk, NY) statistical software.

Results

A total of 472 NSCLC patients were included in the study. The patient Group included 80 women (16.9%) and 392 men (83.1%). The mean age of the patients was 60.53±8.35 (r=26-84) years. One hundred fifty two patients were aged 65 years or over (32.2%) and 320 patients were under 65 years of age (81.5%). Left resection was performed in 190 patients (40.3%), right resection in 282 patients (59.7%). The histologic type was adenocarcinoma in 247 patients (52.3%), squamous cell carcinoma in 205 patients (43.4%), and large-cell carcinoma and adenosquamous cell carcinoma in 20 patients (4.2%). A mean of 17.57±9.08 lymph nodes were removed. The comparison of demographic and histopathological characteristics between the <65 and ≥65 age groups is shown in Table 1.

Nine patients (1.9%) died in the first 90 days. The mean follow-up time was 51 months. The mean survival time was 126 months and the 5-year survival rate was 67.2%. In the univariate analysis, the 5-year survival rate was 55.2% for patients over the age of 65, while this rate was 72% in patients younger than 65 ($p<0.001$). The 5-year survival rate in right-sided resections was 70.1% ($p=0.024$). In terms of histopathology, survival time was significantly longer in squamous cell carcinoma than for other types ($p<0.05$) (Figure 1). The poorest 5-year survival (33.2%) was seen in patients with large-cell and adenosquamous cell carcinomas. Five-year survival rates for patients with Stage IA1, IA2, IA3, and IB tumors were 78.1%, 72.5%, 77.3%, and 56.7%, respectively ($p=0.009$). Patients with tumors 2 cm or smaller had a 5-year survival rate of 76.4% ($p=0.004$ vs. tumors >2 cm) (Figure 2).

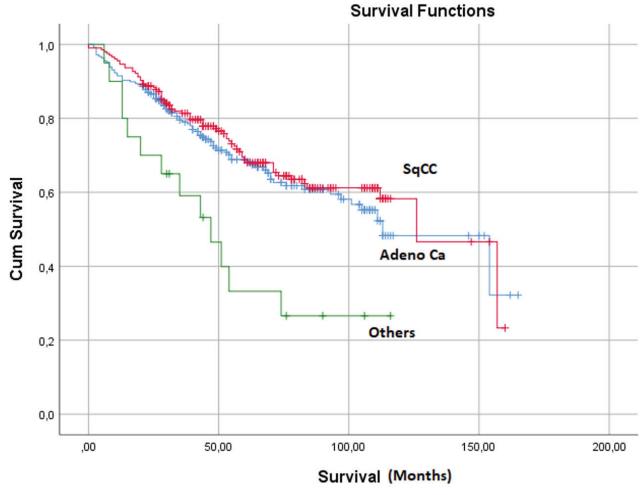

Figure 1. Kaplan-Meier curve of histopathological stage

In multivariate analysis, age ≥65 years, left-sided resection, large cell and adenosquamous cell cancers, and Stage IB tumors were found to be poor prognostic factors. Table 2 presents the analyses of factors affecting mortality.

Discussion

Based on the Stage-based survival data obtained in our study, we recommend that Stage I tumors be divided into those <1 cm and those between 1 and 4 cm. On the 8th edition of the TNM classification for lung cancer, Goldstraw et al. (8) divided Stage I lung cancer tumors into 4 subgroups according to their differences in survival. They determined a statistically significant difference in survival between the groups, with 5-year survival rates of 92% for Stage IA1, 83% for IA2, 77% for IA3, and 68% in IB tumors (8). Aokage et al. (14) also reported 5-year survival rates in the Stage I subGroup as 95% in IA1, 84% in IA2, 76% in IA3, and 65% in IB. Stage IA1 had significantly better survival than the other groups, but there were no significant differences among the Stage IA2, IA3, and IB groups in terms of survival outcomes. Similar to the study by Aokage et al. (14), multivariate analysis in our study revealed a statistically significant difference in survival between Stage 1A1 and 1B but no differences between Stage IB and the other groups. Our survival results different from some of publications in the literature, this is due to the performance status of the patients.

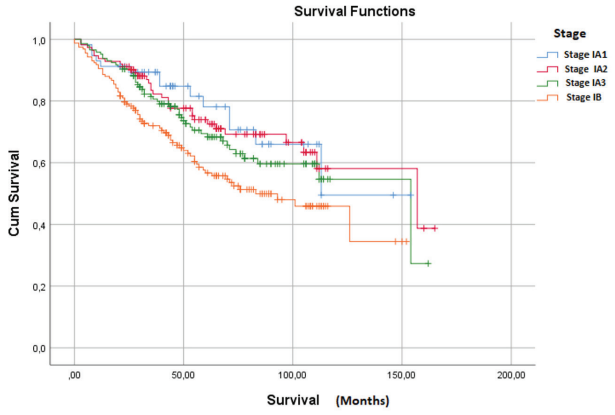

Figure 2. Kaplan-Meier Curve of Stage

Although surgery is considered the gold standard treatment approach in early-stage lung cancer (Stage I-IIA), surgical outcomes in geriatric patients differ compared to those of younger patients. Studies have shown that geriatric patients have poorer survival outcomes compared with younger patients, with this being mainly attributed to

Table 1. Comparison of the demographic and clinical characteristics of the patients by age group

Variable		Group A (<65 years)		Group B (≥65 years)		p
		n	%	n	%	
Sex	Male	264	82.5	128	84.2	0.643
	Female	56	17.5	24	15.8	
Age, years (mean ± SD)		56.10±5.77		69.86±4.26		0.001*
Resection	Segmentectomy	3	0.9	4	2.6	0.111
	Lobectomy	292	91.3	142	93.4	
	Pneumonectomy	25	7.8	6	3.6	
Resection side	Right	191	59.7	91	59.9	0.970
	Left	129	40.3	61	40.1	
Operation	Standard	298	93.1	141	92.8	0.885
	Sleeve	22	6.9	11	7.2	
Histopathology	Adenocarcinoma	168	52.5	79	52	0.753
	Squamous cell carcinoma	137	42.8	68	44.7	
	Other	15	4.7	5	3.3	
Tumor size, cm (mean ± SD)		2.54±0.99		2.54±0.91		0.908
Stage	1A1	40	12.5	17	11.2	0.928
	1A2	74	23.1	38	25	
	1A3	97	30.3	48	31.6	
	1B	109	34.1	49	32.2	
Lymph nodes removed		17.49±8.65		17.70±9.95		0.837

Chi-square tests was used in this table
SD: Standard deviation, * indicate statistical significance (p<0.05)

Table 2. Factors affecting survival

Variables		5-year survival (%)	Median survival (months)	95% CI	Univariate	Multivariate	
					p	HR (95% CI)	p
Age, years	<65	72	154	100-207	0.001	1.92 (1.38-2.65)	<0.001*
	≥65	55.2	98	40-101			
Sex	Male	66	103	89-136	0.157	-	
	Female	71	90	80-100			
Side	Right	70.1	154	100-207	0.024	1.37 (1-1.8)	0.047*
	Left	62.8	97	69-124			
Resection	Lobectomy	67.3	126	95-156	0.334	-	
	Pneumonectomy	61.5	84	64-103			
Histopathology	Adenocarcinoma	68.9	113	87-138	0.004	-	0.001
	SqCC	81.4	126	97-154		0.77 (0.5-1.0)	0.125
	Other	33.2	47	27-66		2.58 (1.4-4.6)	0.002*
TNM Stage (8^{th} ed)	1A1	78.1	113	91-129	0.009	0.57 (0.39-0.38)	0.004*
	1A2	72.5	157	79-234		2288 (0-2.96)	0.836
	1A3	77.3	154	70-237		2022 (0-2.62)	0.840
	1B	56.7	83	56-109		-	0.036
Tumor size	<2 cm	76.4	157	99-214	0.004	481 (0-6.23)	0.822
	>2 cm	62	112	84-139			
Resection type	Standard	67.1	154	95-212	0.992	-	
	Sleeve	69.3	126	47-204			

Kaplan-Meier Survival test was used in this table
CI: Confidence interval, HR: Hazard ratio, SqCC: Squamous cell carcinoma, TNM: Tumor, node, metastasis, * indicate statistical significance (p<0.05)

age-related tissue fragility, physiological changes (reduced performance and respiratory capacity), and surgical risks (11,15-20). Park et al. (3) observed a major difference in survival between geriatric and young patients (5-year survival of 69% vs. 91%, respectively). Differences in 5-year survival between older and younger patients were also reported by Goodgame et al. (21) (52% vs. 67%) and Sigel et al. (22) (63.5% vs. 69.2%). Consistent with the literature, postoperative 5-year survival was poorer among geriatric patients in our study when compared with the younger patient Group (55.2% vs. 72%).

In contrast to other studies in the literature, Cerfolio and Bryant (23) found that 5-year survival was better in their geriatric patient Group than the young patient Group (78% vs. 69%). The differences among these studies may be related to the retrospective design of most studies, differences in the selection of patients for surgical resection, and variation between surgical protocols [sublobar resection (wedge resection, segmentectomy), lobar resection] among clinics. In addition, older age has been associated with poorer survival outcomes even within the geriatric population. In a study conducted in the US, patients over 80 years of age had a 5-year survival rate below 40% (24).

Stereotactic body radiotherapy (SBRT) has been increasingly used in the treatment of geriatric patients with early-stage NSCLC in recent years. However, although SBRT significantly improved survival outcomes in patients who were considered inoperable and those who refused surgical treatment or in clinics that revised the treatment protocol for this patient group, the success rate is still much lower when compared with surgery (16,25). Ruiter et al. (16) compared patients who underwent surgery and those who had SBRT and reported a 5-year overall survival of 62% in the surgery group and 29% in the SBRT group. Successful outcomes have been achieved with SBRT in primary local control of the disease. For example, in the radiation therapy oncology Group 0236 trial, the 3-year primary disease control rate was reported to be 97.6%, and the 3-year survival rate was 55.8% (26). Despite the lower toxicity and better early-stage mortality and survival outcomes reported with SBRT, it has not been able to replace surgery in terms of long-term survival. Of course, the overall performance status, inoperability criteria, and respiratory capacity of patients who underwent SBRT should not be overlooked. When patients who undergo surgery are evaluated in terms of these criteria, they have considerable advantages. In our clinic, we operate on all

patients who have performance capacity amenable to surgery. We expect the ongoing randomized prospective studies on this subject (VALOR, POSTILV) to yield more objective results.

Evaluation of the effect of surgical resection type on survival has produced different results. When the survival rates of lobectomy and pneumonectomy patients in our study were compared, the lobectomy Group had a higher survival rate but the difference was not statistically significant (p=0.334). Similarly, in our previous series we observed no difference in survival between geriatric patients who underwent lobectomy, segmentectomy, and pneumonectomy groups. Additionally, no significant differences in long-term survival and recurrence rates were reported in studies comparing sublobar and lobar resections in early-stage geriatric populations (4). In one such study conducted by Fiorelli et al. (27), the 5-year survival rate among 239 patients was 60.5% in the lobar resection Group and 45% in sublobar resection group, but the difference was found not to be statistically significant (p=0.1). Dell'Amore (28) also reported no difference in survival between lobectomy and sublobar resection patients (p=0.6). However, some authors argue that pneumonectomy adversely affects mortality and long-term survival outcomes compared to other resection types (29-31). In the study by Goodgame et al. (21), the pneumonectomy Group had the highest rate of perioperative mortality. In addition, the pneumonectomy Group exhibited significant differences in terms of recurrence and overall survival (p=0.0003, p=0.043, respectively). It was argued that survival rates were low because pneumonectomy increases perioperative mortality and considerably increases the rate of postoperative complications in geriatric patients. We believe that the discrepant results of these studies can be attributed to factors such as surgical technique and surgeon experience, differences in preoperative evaluation, heterogeneous patient groups, postoperative rehabilitation, the method of selecting suitable candidates for the resection types, and neoadjuvant/adjuvant treatment protocols.

Most survival studies in the early-stage NSCLC geriatric patient population have reported better histopathological outcomes in the adenocarcinoma Group (11,32,33). In their study of 1116 patients, Ganti et al. (34) detected a significant difference in survival in the adenocarcinoma group. A multivariate analysis conducted by Bei et al. (11) showed adenocarcinoma to be an independent factor of better prognosis in early-stage octogenarians. Hino et al. (35) included all Stage groups in their evaluation and determined that patients with adenocarcinoma had a significantly higher survival rate than the other groups (p=0.016). In other studies, similar survival outcomes were reported in all histopathology groups (adenocarcinoma, squamous cell carcinoma, large-cell) [Dell'Amore et al. (28), 2014; Razi et al. (36), 2016]. In contrast to these studies, multivariate analysis in our study indicated that the large-cell and adenosquamous cell Group had the poorest prognosis in terms of overall survival. There was no statistically significant difference between adenocarcinoma and squamous cell carcinoma.

Study Limitations

Potential sources of bias in this study include the retrospective study design and the smaller proportion of women in the study sample. Furthermore, the operations included in the analysis were performed by different surgeons, and the patients' performance status was not evaluated. Another shortcoming of this study is that disease-free survival was not calculated for these patients.

Conclusion

Advanced age is an important prognostic factor in stage I lung cancer. Early-stage large-cell and adenosquamous cancer have the worst prognosis. There was no difference in survival between adenocarcinoma and squamous cell carcinoma in this study. Based on our results, we believe that revision of the Stage I classification is warranted in the next edition of the TNM staging. However, more comprehensive multi-center studies on this subject are still needed.

Authorship Contributions

Concept: M.V.D., C.B.S., A.A., S.E., M.E., A.O., M.M., Design: M.V.D., C.B.S., V.E., C.A., Data Collection or Processing: M.V.D., C.B.S., V.E., C.A., A.A., S.E., M.E., A.O., M.M., Analysis or Interpretation: M.V.D., C.B.S., Literature Search: M.V.D., C.B.S., A.O., M.M., Writing: M.V.D., C.B.S., A.O., M.M.,

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Original Article

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Relationship of Frontal Cortex Glucose Metabolism with Depression-Anxiety Status in Patients with Early Stage Non-Small-Cell Lung Cancer: A Cross-Sectional Study

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Abstract

Aim: We investigated the relationship between frontal cortex 18-fluorodeoxyglucose (^{18}FDG) uptake levels and depression-anxiety status in patients with early-stage non-small-cell lung cancer (E-NSCLC) who underwent ^{18}FDG-positron emission tomography/computed tomography (^{18}FDG-PET/CT) imaging.

Methods: This prospective study was conducted between the May-November 2020, after the permission of ethics committee. A total of 34 patients with E-NSCLC who underwent ^{18}FDG-PET/CT imaging for diagnosis-staging and the control group consisting of 25 subjects were included in the study. Regional cerebral ^{18}FDG uptake level was calculated by SUVmean. Depression-anxiety levels were determined using Hospital Anxiety and Depression Scale (HADS). The frontal cortex SUVmean ratio and depression-anxiety levels was compared between the groups, and the relationship between SUVmean ratio and depression-anxiety levels were performed.

Results: The frontal cortex SUVmean ratio values were somewhat lower in the patient group compared to the control group for both sexes, being more prominent in males. However, these differences were not statistically significant for both sexes [for male: 0.75±0.006, 0.79±0.03; (p=0.055); for female: 0.73±0.04, 0.74±0.049; (p=0.71)]. In addition, a statistically significant weak negative correlation was found between frontal SUVmean values and anxiety levels in male patients (r=-0.4697, p=0.01).

Conclusions: We believe that the measurement of frontal cortex ^{18}FDG uptake level and notification of the clinician about the patients with decreased values are important in patients with E-NSCLC who underwent ^{18}FDG-PET/CT imaging.

Keywords: Positron emission tomography/computed tomography, carcinoma, non-small-cell lung, depression, anxiety

Introduction

Depression is known to be more commonly seen in those with cancer or other chronic additional diseases (1,2). More common depressive disorders have been reported to occur especially in pancreas, breast and lung cancers (2). Although there is many evaluation scales that can be used for the diagnosis and screening of depression such as beck depression test, Hospital Anxiety and Depression Scale (HADS), patient health questionnaire (DSM-MD4), center for epidemiologic studies depression scale (CES-D), Hamilton Depression Rating Scale; since depression symptoms are similar to the general condition in cancer patients, it may be difficult to diagnose. The treatment of accompanying depression has been reported to provide a positive contribution on the prognosis and survival in cancer patients (2-4).

18-fluorodeoxyglucose-positron emission tomography/computed tomography (^{18}FDG-PET/CT) is an imaging method evaluating glucose metabolism, and today is widely used in many clinical indications, especially in the field of oncology. Since the main energy need of the cerebral tissue is glucose, and because physiologically high level of ^{18}FDG uptake is seen, most centers perform the imaging from the skull base in the oncologic ^{18}FDG-PET/

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CT studies. But some centers as in our center perform the imaging from the vertex and the cerebral tissue is included in the imaging area. In this way, some incidental cerebral-cerebellar lesions and diseases may be detected in oncologic ^{18}FDG-PET/CT examines.

Although there are studies showing high frequency of depression in cancer and negative effects on prognosis-survival, there are few studies examining brain ^{18}FDG uptake levels in lung cancer (5,6). In addition, looking at the literature, no study was found investigating the relationship between the presence of depression and cerebral ^{18}FDG uptake levels in early-stage (Stages 1-2) lung cancer (E-NSCLC).

In the light of this information, we aimed to investigate the relationship between frontal cortex ^{18}FDG uptake level and depression-anxiety status in patients who underwent ^{18}FDG-PET/CT imaging and were clinically accepted to have E-NSCLC, to compare the results with the control group and to evaluate whether ^{18}FDG uptake can be a helpful parameter in predicting the diagnosis of depression in E-NSCLC.

Methods

Subjects

The patient information form was filled in for this study and the approval of the institutional ethics committee was obtained from Gaziantep University (number; 2020-152, date; 15/04/020). This prospective study was conducted between May and November 2020, after the permission of the ethics committee. A total of 34 patients with 25 being males and 9 females who underwent ^{18}FDG-PET/CT for the diagnosis and/or staging in our clinic and accepted to have early-stage (Stages 1-2) lung cancer ^{18}FDG-PET/CT and chest CT findings were included in the study. In addition, a total of 25 persons with 16 being males and 9 females who underwent ^{18}FDG-PET/CT due to any cancer suspicion in our clinic and without any malignancy detected were assigned to the control group. When establishing the control group, it was paid attention to be similar to the patient groups' features as age, gender, profession, educational status.

Newly diagnosed patients who did not receive any treatment (radiotherapy, chemotherapy, surgery), were histopathologically diagnosed with non-small-cell lung cancer (NSCLC), and accepted as to have early-stage (Stages 1-2) lung carcinoma on ^{18}FDG-PET/CT and chest CT findings, and persons without any pathological ^{18}FDG uptake detected as the control group were included in the study.

Patients with a known pathology/drug use/surgery that could affect cerebral-cerebellar ^{18}FDG uptake, pregnant and breastfeeding patients and those aged under 18 years were excluded from the study.

Patient Preparation and ^{18}FDG-PET/CT Imaging Protocol

The blood glucose of the patients was cotrolled the following 12-hour fasting and if glucose level <150 mg/dL, were injected with 5 MBq/Kg intravenous (iv) ^{18}FDG.

The PET/CT imaging was performed 60 minutes after the injection using combined PET/CT device (Biograph2 LSO/Somatom Emotion; Siemens Medical Solutions) in our department.

The imaging was performed as whole-body from vertex up to the upper thigh region at mean 5-7 bed interval.

Imaging Analysis and Evaluation of the Patients

^{18}FDG-PET/CT images of the patient and control groups included in the study were evaluated by two experienced nuclear medicine specialists. Frontal cortex ^{18}FDG uptake level was found by calculated by averaging ratios of the mean standard uptake values (SUVmean) taken from the superior, middle and inferior levels of the frontal cortex area to the SUVmean measurements taken from the other cerebral regions in similar sections.

Liver SUVmax values were also measured in order to test the possible variabilities related to the other factors that could affect FDG uptake in the body.

Depression-anxiety levels of the persons in the patient and control groups who met the inclusion criteria were determined 2 days after ^{18}FDG-PET/CT imaging using HADS, which validity and reliability was studies by Aydemir et al. (7), by a psychiatrist who was blind to ^{18}FDG-PET/CT findings.

The HADS scale consisted of 14 questions with anxiety was measured with seven (uneven-number items: 1, 3, 5, 7, 9, 11 and 13) and depression with seven (even-number items: 2, 4, 6, 8, 10, 12 and 14) questions. The answers were scored with 0-3 points and the minimum score that can be obtained from the scale was 0 and the maximum score was 21 points. As specified in the study by Aydemir et al. (7), cut-off points for the Turkish form of the scale was taken as 10 points for anxiety (HADS-A) and 7 for depression (HADS-D).

Both groups were examined in terms of age, gender, profession, educational level, blood glucose, frontal cortex SUVmean ratio, depression and anxiety levels.

The relationship between frontal cortex SUV mean ratio and depression-anxiety levels was analyzed.

Statistical Analysis

Data of the patient and control groups were obtained via the medical history, HADS scale and ^{18}FDG-PET/CT images. Data were analyzed using SPSS v.18 statistical software. Mean, standard deviation and percentage descriptive values were used for age, blood glucose levels, liver SUVmax, frontal cortex SUVmean and HADS scale

results. Quantitative variables were expressed as mean ± standard deviation (SD) when normally distributed, and as [IQR, (interquartile range)] when non-normally distributed. The comparison between the groups was made with t-tests, Fisher Exact and chi-square tests. Pearson's analysis was used to determine the correlation between frontal cortex SUVmean values and HADS scores. The $p<0.05$ were considered statically significant for all statistical tests.

Results

Demographic features (age, gender, profession, educational status), frontal cortex SUVmean, HADS-A and HADS-D results of the patient and control groups, intergroup comparisons of these parameters and statistical analysis data are given in Table 1,2, and these data were explained shortly with the following sentences.

There was no statistical difference between the two groups in terms of age, gender, profession, educational status, blood glucose levels and liver SUVmax values ($p>0.05$).

Frontal cortex SUVmean ratios were slightly lower in both sexes in the patient group compared to the control group, although the difference was not statistically significant ($p>0.05$).

The correlation between frontal cortex SUVmean values and HADS-A and HADS-D scores was analyzed in the patient group, and a statistically significant weak negative correlation was found between frontal cortex SUVmean values and HADS-A in the male patients group ($r=-0.4697$, $p=0.01$), while no statistically significant correlation was found in the other sex and scores.

Figure 1 shows fusion ^{18}FDG-PET/CT images of a patient with decreased frontal cortex FDG uptake (SUVmean ratio: 0.68) compared to the control group who a HADS-A score of 12 and a HADS-D score of 9, while Figure 2 shows fusion ^{18}FDG-PET/CT images of a patient with normal frontal cortex FDG uptake (SUVmean ratio:

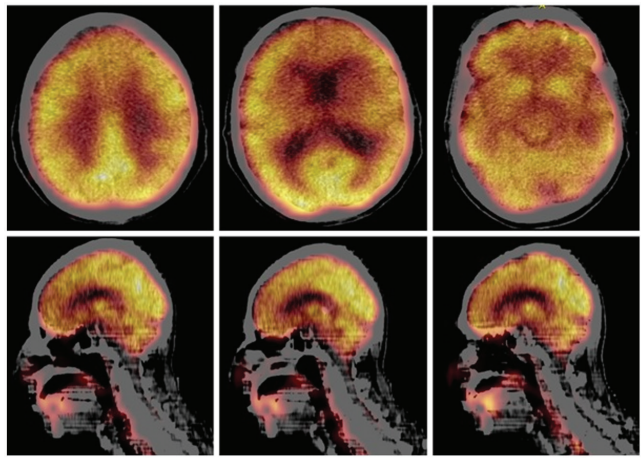

Figure 1. Cranial FDG-PET/CT fusion images of a 59-year-old male patient (top row: transaxial sections from the vertex towards inferior; bottom row: sagittal sections): Frontal cortex FDG uptake appears to be decreased (Frontal cortex SUVmean r=0.68). HADS-A and HADS-D scores were found 12 and 9, respectively.
FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV: Standart uptake value, HADS-A: Hospital anxiety and depression scale-anxiety, HADS-D: Hospital anxiety and depression scale-depression

Table 1. The Patient and control groups' characteristics

Characteristics	Male patients	Male control	p	Female patients	Female control	p
Subject number	25	16	p*=0.56	9	9	p*=0.56
Age (year)	57.8±7.2	55.1±5.9	p**=0.22	53.8±7.8	52.7±6.6	p**=0.74
Education level (↓/↑)	12/13	6/10	p*=0.53	7/2	6/3	p***=0.53
Profession (working or retired/not working)	24/1	15/1	p*=1.0	8/1	7/2	p***=0.52

Education level ↓: High school or below, Education level ↑: University, p*: Fisher's Exact test, p**: T-test, p***: Chi-square test

Table 2. The Inter-group comparison for the metabolic findings and anxiety-depression scores

Data	Male patients	Male control	p	Female patients	Female control	p
Glucose level (mg/dL)	117.8±12.5	112.9±14.0	p*=0.25	113.3±12.4	111.7±13.7	p*=0.80
Liver SUVmax	3.37±0.43	3,28±0.51	p*=0.27	3.30±0.37	3.23±0.36	p*=0.35
Frontal cortex SUVmean ratio	0.75±0.06	0.79±0.03	p*=0.055	0.73±0.04	0.74±0.04	p*=0.71
HADS-A score	9.7±3.6	8.5±2.7	P*=0.28	10.8±4.3	9.2±2.5	p*=0.33
HADS-D score	5.8±1.7	5.1±1.5	p*=0.18	7.3±2.0	6.8±1.7	p*=0.62
Correlation of SUVmean and HADS-A	r=-0.4697	-	p**=0.01	r=-0.4813	-	p**=0.18
Correlation of SUVmean and HADS-D	r=-0.3754	-	p**=0.06	r=-0.5303	-	p**=0.14

SUV: Standart uptake value, HADS-A: Hospital anxiety and depression scale-anxiety, HADS-D: Hospital anxiety and depression scale-depression, p*: T-test, p**: Pearson correlation analysis

0.81) compared to the control group who a HADS-A score of 9 and a HADS-D score of 6.

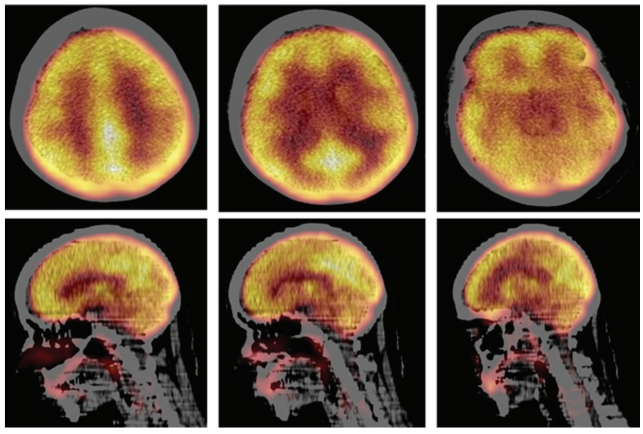

Figure 2. Cranial FDG-PET/CT fusion images of a 46-year-old female patient (top row: transaxial sections from the vertex towards inferior; bottom row: sagittal sections): There is no decrease in frontal cortex FDG uptake and it is appear to be normally (Frontal cortex SUVmean r=0.81). HADS-A and HADS-D scores were found 9 and 6, respectively.
FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, SUV: Standart uptake value, HADS-A: Hospital anxiety and depression scale-anxiety, HADS-D: Hospital anxiety and depression scale-depression

Discussion

Although establishing the diagnosis of depression is difficult in cancer patients due to similarity between general status features and depression symptoms, there are studies in the literature demonstrating high incidence and negative effects of depression on prognosis in patients with lung cancer (3,8-11). On the other hand, the number of studies investigating cerebral FDG uptake levels and the relationship between the presence of depression and cerebral FDG uptake in patients with lung cancer is limited (5,6). In our study, we compared frontal cortex FDG uptake between patients with non-small cell lung carcinoma and the control group, and investigated its relationship with HADS-A and HAS-D scores. In this respect, our study is the first in the literature.

Many factors such as age, gender, occupation, educational status, PET imaging procedure-parameters, blood glucose level, possible drugs used, neurological-vascular-systemic diseases can cause changes in brain FDG uptake. In order to minimize these, maximum attention was paid to ensure inclusion-exclusion criteria of the study and to be no statistical differences between the patient-control group in terms of these factors.

Because the probability of unpredictable metastases to distant organs such as the brain in small cell lung carcinoma, and high probability of cerebral metastasis in advanced stage lung cancer, we were included only patients with E-NSCLC in our study. When reviewing of few studies (5,6) which evaluating brain ^{18}FDG uptake in patients with lung cancer in the literature, it is seen that they are designed without regard to case discrimination, and therefore we believe that our study is superior in this sense.

Although ^{18}FDG uptake is physiologically high in the cerebral tissue, the imaging is started from the cranial vertex in ^{18}FDG-PET/CT examinations in some centers, and although procedures-parameters in neuropsychiatric cerebral ^{18}FDG-PET/CT examinations are not used, incidental cerebral-cerebellar metastases, CVD and demantial pathologies may be detected. Similarly, we are routinely include the brain to imaging area on PET examinations and we would like to emphasize that no additional imaging was performed except for routine imaging in our study.

It is argued that regional increases and decreases in cerebral FDG intake of cancer patients are caused by the interaction between central neuromodulation and tumor-associated peripheral reaction. In the study conducted by Zhang et al. (5), brain regions where decreases/increases in FDG uptake in small cell lung cancer patients were identified and possible mechanisms were investigated. Whereas in our study only frontal lobe FDG uptake levels were investigated, and the other cerebral regions could not be examined. The most important reason for this was the lack of a software specific to cerebral studies such as cortexID and NeuroQuant, and not performed the neurologic PET/CT examination which containing differing imaging procedures-parameters.

Although evaluating only frontal lobe FDG uptake may be seen as a weak aspect of our study, there are studies showing that prefrontal dysfunction is the pathologic basis of depression onset and also a marker of a depressive condition (12,13). In addition, it has been reported that frontal and parietal regions are the main components of the dorsal attention network (DAN), which controls attention allocation and spatial orientation functions, and these may be associated with possible dysfunction in cancer patients (6,14,15). In the present study, although no statistically significant difference was not found between both sexes in the patient group compared to the control group in terms of frontal cortex FDG uptake, it was lower in the patient group than in the controls, and these findings were supporting the literature.

Clinical examination is necessary for the diagnosis of depression, although HADS is a simple, but simple, reliable

depression evaluating tool designed for use in medical practice. Studies have shown that this scale can be used not only for hospital setting, but also social and first line medical applications. The reason for using this scale in our study was that the study group was in the hospital, the scale can be used in a practical way in about five minutes and validity-reliability study of the scale was conducted for our population.

HADS-A and HADS-D scores were found to be higher for both sexes in the patient group compared to the control group. However, these differences were not statistically significant. It should be taken into account that, this result might be resulted from that although the control group consisted of the persons without pathologic ^{18}FDG uptake detected, this group could not be created with completely healthy persons without health problems and/or our patient group consisted of the patients with early-stage (Stages 1-2) disease.

When the relationship between the frontal cortex SUVmean values, HADS-A and HADS-D scores was analyzed in the patient group, there was a statistically significant weak negative correlation between frontal cortex SUVmean values and HADS-A scores only in the male patients group. Although a weak correlation was found only in male patients group and the study group and assessment scale were different, in a study by Fu C et al. (16) it was reported that SUV values were low in ^{18}FDG/PET-CT imaging in the frontal gyrus region and showed correlation with the Hamilton score in major depressive patient compared to the control group.

Although the HADS scale has been performed 2 days after ^{18}FDG/PET-CT imaging in the patient and control groups opened the door for critical opinion that anxiety-depression evaluation was not made concurrently, we think that this provided an advantage of ruling out concern-fear state that can be caused by the imaging process.

Study Limitations

Besides being the first prospective cross-sectional study conducted in this area, our study also has some main limitations. These can be listed as follows; the presence of depression could not be determined with clinical evaluation, some software evaluating cerebral metabolism in a more standardized way could not be used and the number of patients was relatively small.

Conclusion

We found that the frontal cortex ^{18}FDG uptake was lower in the patient group than in the controls and, there is a relationship between the frontal cortex SUVmean values and HADS-A scores in male patients. We think that it is important to measure frontal cortex ^{18}FDG uptake in NSLC patients who underwent ^{18}FDG-PET/CT imaging and to inform the clinician about the patients with decreased ^{18}FDG uptake values of the frontal cortex for the prediction of likely depressive status.

Authorship Contributions

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

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

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Original Article

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Social Appearance Anxiety in Patients with Acne Vulgaris: A Cross-Sectional Controlled Study

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Abstract

Aim: The purpose of our study is to identify the extent to which acne vulgaris patients with facial involvement are affected by this condition which may negatively affect the self-perception of individuals.

Methods: A total of 122 acne vulgaris patients with facial involvement between the ages of 18-65 and 115 healthy controls that were matched in terms of age, gender and educational status have included in the study. Patients and healthy controls were asked to fill in social appearance anxiety scale (SAAS) and hospital anxiety depression scale, and dermatology life quality index and visual analog scales were applied to the patient group. The study was designed as a cross-sectional controlled study which is a type of observational study. The data of this study were collected among those who applied to the dermatology outpatient clinic between 01.03.2020-01.10.2020. The control group was selected from the hospital staff who were healthy and volunteers.

Results: Average SAAS scores of the patient, and the control group were 55.20, and 19.70 points, respectively. Thus, the average SAAS score of the patient group was found to be significantly higher than that of the control group ($p<0.01$).

Conclusion: Acne lesions in acne vulgaris patients that appear on visible skin surfaces cause anxiety in individuals due to their appearance. This condition revealed that those with acne lesions should undergo psychiatric as well as dermatological treatments.

Keywords: Acne vulgaris, anxiety, depression, social appearance anxiety

Introduction

Acne vulgaris is a chronic inflammatory dermatosis with predilection on the face and upper body, predominantly areas populated with pilosebaceous units. Depending on the clinical severity in patients, it may manifest itself with erythematous papules and pustules, comedones, nodulocystic lesions and scarring (1). Its four main etiopathogenetic factors are increased sebum manufacture, extreme cornification of the pilosebaceous canal, microbial habitats and inflammation (2).

Acne vulgaris is one of the most common dermatoses, and the relationship between acne and psychological factors has been investigated for many years. Existing lesions in acne patients may worsen with emotional stress, and psychological and psychiatric problems may develop in patients with the exacerbation of the lesions (3). In some case series, patients with acne vulgaris accompanied by psychological diseases like anxiety, depression, suicidal thoughts have been reported (4). It is believed that anxiety is a factor that worsens the disease in 74% of acne patients (5). Some studies have found increased frequency of anxiety in diseases with acne vulgaris, and a direct proportion among the severity of anxiety and the seriousness of acne has been indicated (1).

Undoubtedly, the most can be seen and widest organ of our body is the skin. It significantly affects the physical appearance. To have a healthy skin structure plays an important role in preserving the physical, mental, inner and social welfare of the individual. The face is an important part of your body with regard to human attractiveness to the counter sex (6). As a result, dermatoses, especially on the face, may cause deterioration of physical and mental health, low self-esteem, trouble and disturbances in social interplays (7). Difficulties that social appearance anxiety (SAA) may cause in the lives of patients with acne vulgaris

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can lead to loss of workforce, problems in family and most importantly, in social relationships. In this study, we have researched the effects of acne vulgaris on anxiety levels of patients caused by their social appearance.

Methods

Study Design and Patient Evaluation

The required written permissions of the study were obtained from Medical Faculty at Van Yuzuncu Yil University Hospital Ethics Committee and the participants with the decision number 2020/02-10 and date 21/02/2020. Volunteered participants who signed informed consent forms were enrolled in the study

The study was designed as a cross-sectional controlled study which is a type of observational study. The data were collected among those who applied to the dermatology outpatient clinic between 01.03.2020-01.10.2020. The control group was selected from the hospital staff who were healthy and volunteers. A total of 122 acne vulgaris patients with facial involvement between the ages of 18-65 and 115 healthy controls that were matched in terms of age, gender, and educational status have included in the study.

Patients and healthy controls were asked to fill in SAA scale (SAAS) (8) and hospital anxiety depression (HAD) (9) scale, and dermatology life quality index (DLQI) (10) and visual analog scales were applied to the patient group.

Statistical Analysis

Descriptive statistics were used to sum up the demographic and clinical characteristics of the case and control groups. The cruciality of the differences between the two groups was assessed by an independent sample t-test. The Pearson correlation test was adjusted to calculate correlations between variables. Statistical analysis was carried out using the SPSS 22.0 statistical package, and the level of significance have set at $p<0.05$.

Results

Hundred and twenty-two acne vulgaris patients (46 men, and 76 women) and 115 control subjects (49 men, and 66 women) were included in the study. The mean ages of acne patients, and the control group were 25.844±6.354, and 25.80±5.713 years, respectively. The age, gender, marital status, educational status, occupational and other sociodemographic data of the groups are given in (Table 1).

According to the consequence of the t-test; any important difference was not observed between acne vulgaris and control groups. With regard to age and gender distribution, but the HAD anxiety subscale, HAD depression subscale and SAAS values were found to be important higher in the patient group relative to the control group ($p<0.05$) (Table 2).

The difference between the patient and control groups with regard to mean SAAS scores was found to be statistically important. The mean SAAS score of the patient group was found to be rather higher relative to the control group ($p<0.01$) (Table 2).

The difference between the case and control groups with regard to the mean HAD depression subscale scores was found to be statistically significant. The mean HAD depression subscale scores of the patient group was found to be higher than the control group ($p<0.05$) (Table 2).

The correlation coefficient between the SAAS scores and the HAD anxiety subscale scores was 0.753 (75.3%) which indicated the presence of statistically significant

Table 1. Socio-demographic data of the patient, and the control groups

		Acne vulgaris group (n=122)	Control goup (n=115)
Age	(Years) (Mean ± SD)	25.844±6.354	25.80±5.713
Gender	Male [n (%)]	46 (37.7)	49 (42.6)
	Female [n (%)]	76 (62.3)	66 (57.4)
Marital status	Married	63 (51.6)	51 (44.3)
	Single	59 (48.4)	64 (55.7)
Educational status	Primary school	48 (39.3)	39 (33.9
	High school	10 (8.2)	10 (8.7)
	University	64 (52.5)	66 (57.4)
Occupation	Student	49 (40.2)	41 (35.7)
	Unemployed	10 (8.2)	9 (7.8)
	Housewife	38 (31.1)	37 (32.2)
	Civil servant	25 (20.5)	28 (24.3)
Smoking status	Smoker	78 (63.9)	61 (53)
	Non-smoker	44 (36.1)	54 (47)
Alcohol use	Yes	14 (11.5)	27 (23.5)
	No	108 (88.5)	88 (76.5)
Chronic disease	Yes	36 (29.5)	33 (28.7)
	No	86 (70.5)	82 (71.3)

SD: Standard deviation

Table 2. Descriptive statistics and comparison results

	Patient n (Mean ± SD)	Control n (Mean ± SD)	p
SAAS score	122 (55.2±9.1)	115 (19.7±8.3)	0.001
HAD anxiety subscale score	122 (8.7±3.8)	115 (7.1±2.8)	0.001
HAD depression subscale score	122 (8.2±3.0)	115 (7.3±2.2)	0.014

SAAS: Social appearance anxiety scale, HAD: Hospital anxiety depression scale, SD: Standard deviation

relationship (p<0.01). In other words, when the SAAS scores of the individuals in the patient group increased, the HAD anxiety scores also increased (Table 3).

The correlation coefficient between the SAAS scores and the HAD depression subscale scores was 0.499 (49.9%) which indicated the presence of a statistically significant relationship (p<0.01). In other words, when the SAAS scores of the individuals in the patient group increased, the HAD depression scores also increased.

The correlation coefficient between the SAAS score and the DLQI have 0.409 (40.9%) which indicated the presence of a statistically significant relationship (p<0.01). In other words, as the SAAS scores in the patient group increased, DLQI values also increased (Table 3).

The correlation coefficient between the SAAS and the Visual Analogue Scale (VAS) was 0.605 (60.5%), which indicated the presence of a statistically significant relationship (p<0.01). In other words, when the SAAS values of the individuals in the patient group increased, the VAS values also increased (Figure 1) (Table 3). Correlation in the control group was indicated in Table 4.

Table 3. The correlation coefficient between the parameters in patient group

		SAAS	HAD ank	HAD dep	DLQI	VAS
SAAS scores	Pearson korelasyon p value	1	-	-	-	-
HAD anxiety subscale	Pearson korelasyon p value	0.75 0.01	1	-	-	-
HAD depression subscale	Pearson korelasyon p value	0.49 0.01	0.77 0.01	1	-	-
VAS	Pearson korelasyon p value	0.6	0.77	0.57	0.88	1

SAAS: Social appearance anxiety scale, HAD: Hospital anxiety depression scale, DLQI: Dermatology life quality index, VAS: Visual analog scala

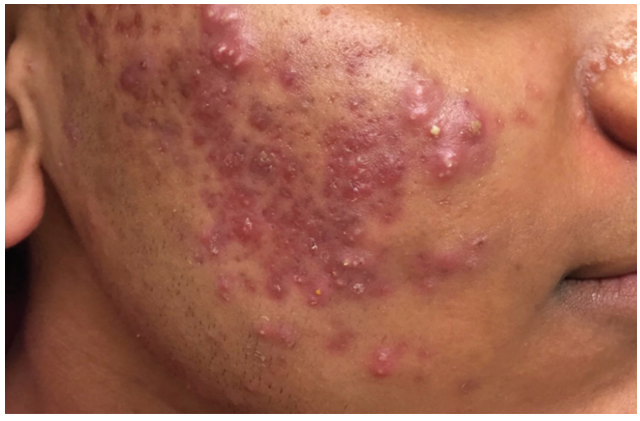

Figure 1. Patient with papules and pustules with nodulo-cystic structures in both malar areas (nodulocystic acne). The picture was shared with the permission of the patient.

Table 4. Correlation coefficient between the parameters in the control group

		SAAS	HAD ank	HAD dep
SAAS scores	Pearson korelasyon p value	1	-	-
HAD anxiety subscale	Pearson korelasyon p value	-0.025 0.790	1	-
HAD depression subscale	Pearson korelasyon p value	-0.002 0.980	0.505 0.000	1

SAAS: Social appearance anxiety scale, HAD: Hospital anxiety depression scale

Discussion

In our present study, first of all, the patient group and the healthy control group were compared. The anxiety level of the group with acne stemming from social appearances was higher than that of healthy individuals. We found that the lesions of the patients on visible areas such as forehead, cheeks and chin significantly increased the anxiety rates.

Many dermatological illnesses can cause psychological morbidity besides physical findings. While there are many works on psychiatric morbidity in dermatology patients, the anxiety levels of acne vulgaris patients stemming from their social appearance have not been emphasized yet.

The appearance of the skin is extremely important for the individual's self-image and social interaction (11). Acne can cause psychosocial burden as well as physical deterioration (12). It has been stated that patients with moderate and severe acne have impaired body image perception, create low self-perception and avoid social activities that require performance (13).

In previous studies, it was found that acne was associated with social isolation, shyness, decreased self-esteem, suicidal thoughts, anxiety and depression, and these symptoms were observed to decrease and disappear as a result of treatments for acne (3). In one study participants' social appearance anxiety, perceived acne severity and acne's impacts on their lives were inversely proportional to their quality of life. However, the perceived acne severity and acne's impacts on their lives were directly proportional to their SAA (14). While some studies show that the presence of acne aggravates anxiety, some others have not found any correlation (15).

In our study, when the patient and control groups were compared, it was found that the patients' predisposition to anxiety and depression increased. In a meta-analytical

review evaluating 42 studies investigating the relationship between acne vulgaris and depression and anxiety, it has reported that acne had a strong relationship with psychiatric symptoms (16). This evaluation supports the results we found in our study.

Fifty-five percent of acne cases reported a close chronological relationship among emotional stress attacks and exacerbation of acne. In a larger study, the researchers stated that the cause of acne was stress in 50% of adult female acne patients (17,18). A small-scale study involving adult patients found that during stressful periods, acne may worsen in these patients. In addition, changes in acne intensity are highly associated with increased stress, proposing that emotional stress from outside sources can have an important effect on acne (19).

In some reviews, it has been stated that the skin and nervous system originate from a common embryological origin, that is ectoderm, and therefore the idea that the two systems are in close relationship and similar hormones and neuropeptides are involved in both systems has been suggested (20,21). Therefore, dysfunction in one of these two systems with the same origin is expected to affect the other (21,22). The fact that 33.4% of patients with dermatological diseases have a concomitant psychiatric disorder explains this situation (23).

Since it has been hypothesized that the skin shares some similar property with the central nervous system stress reaction, and the hypothalamic-pituitary-adrenal (HPA) axis, more data on the causal link among emotional stress and acne can come from *in vitro* laboratory studies (23). If the skin has a HPA- equivalent pathway, it may be easier to understand the impact of psychological stress on certain skin conditions, including acne vulgaris (24).

In individuals diagnosed with acne vulgaris, some behavioral strategies are developed, such as avoiding being the center of attention in the opposite sex or in social environments, and avoiding eye contact, especially if tacne lesions are located on areas that may affect the body image of the person, such as the hands and face (25). In a recent study, 543 patients with perioral dermatitis, acne, folliculitis and rosacea in the facial area were compared with 497 healthy volunteers in terms of psychiatric symptoms such as anxiety and depression. Among the compared facial dermatoses, the highest anxiety and depression scores were found in acne patients (26).

Many studies have shown that acne has a negative effect on quality of life (7,27,28). It has been reported that the presence of psychiatric symptoms is a strong determinant of impairment in quality of life in various dermatological diseases (29,30). The patient's self-perception triggers some psychological symptoms and may determine clinical features. The VAS scale used in our study is a method by which the patient subjectively measures the severity of acne. In our study, it was found that the VAS values of the patients increased in parallel with their SAAS scores. In our study, it was also found that the SAAS scores which reflect the anxiety stemming from the social appearance of the patients, increase in correlation with the DLQI, HAD depression and HAD anxiety values.

Study Limitations

Since the SAAS and the HAD are self-report scales, subjective values will be obtained depending on the capacity of the participants and their education level. Furthermore, due to the insufficient number of patients in the patient group, the patients could not be classified according to the severity of the disease. Since our study is a cross-sectional study, it is difficult to make general inferences. The findings of the study are valid only for the university students where the study was conducted, the results may be different for individuals with different education levels and different ages. Larger studies are needed to figure out the relationship between SAA and acne vulgaris. However, the study was thought to be valuable in terms of revealing the relationships between acne vulgaris, social appearance anxiety.

Conclusion

Acne vulgaris should be considered as a disease that can affect mental health because it causes anxiety disorder caused by the social appearance of the patients. While treating patients for acne vulgaris, psychologica support should also be provided. Although acne is not associated with serious morbidity and mortality or physical disability, it may have significant psychological and social consequences. To reduce the psychosocial impact of acne vulgaris, psychological screening as well as acne treatment can be considered as a necessity. With a good acne treatment, reducing the anxiety levels of the patients due to their social appearance and strengthening their self-perception can increase the quality of life of these patients.

Authorship Contributions

Concept: F.K., Design: F.K., Data Collection or Processing: K.T., Analysis or Interpretation: G.O.Y, Literature Search: F.K., Writing: F.K., K.T.

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

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Original Article

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Assessment and Management of the Dermatological Side Effects of Direct-Acting Antiviral Agent Groups Used in the Treatment of Hepatitis C: A Prospective Study

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Abstract

Aim: As skin disorders may be observed with Hepatitis C, direct-acting antiviral drugs (DAA), dermatological side effects are also reported. The objective is to determine the dermatological side effects of DAA drugs.

Methods: A study was conducted with chronic hepatitis C patients who used Ombistavir/Paritaprevir/Ritonavir + Dasabuvir (Group 1), Sofosbuvir + Ledispavir (Group 2), and sofosbuvir (Group 3) and who supplied the drugs from our hospital. Skin examinations of the patients regarding dermatological side effects were conducted. Patients with dermatological side effects and treatment modalities were followed.

Results: One hundred twelve patients were using Group 1; 69 were using Group 2, 19 were using Group 3. All pruritus patients were in Group 1. It was detected in 56 of 200 patients (28%). Pruritus was more prevalent in patients with diabetes mellitus, hypertension, and heart disease, and the drug could be tolerated in those with no additional systemic comorbidities. Thirty-one patients had renal failure, and 17 of them underwent renal transplantation, and the pruritus rate was high (57%) in the chronic renal disease Group.

Conclusion: Pruritus is the most common side effect observed with DAA drugs used in treating hepatitis C and elderly patients, and patients with comorbidity and renal transplantation are at high risk.

Keywords: Hepatitis C, antiviral agents, pruritus, cutaneous

Introduction

Hepatitis C virus (HCV) is a severe human pathogen with a prevalence of 0.2-4% in different countries. Every year, 3-4 million new hepatitis C cases are detected, and it is thought that 185 million people in total are affected by HCV (1,2). In Turkey, anti-HCV positivity is between 0.6-1.6%, and chronic hepatitis is one of the most important causes of liver cirrhosis and hepatocellular carcinoma (3,4). In Turkey, it is considered that there are 1-1.3 million people infected by HCV (5,6). The objective of chronic hepatitis C treatment is to completely eradicate the virus. The frequent mutation and the availability of multiple genotypes of the virus make it challenging to find a vaccine, affecting treatment success. While peg-interferon and ribavirin are included in the classical treatment of chronic HCV, recently direct-acting antiviral (DAA) regimens for HCV infection has revolutionized its treatment by producing a sustained virologic response of more than 95% in the general population (7-9). Direct-acting antivirals Ombistavir/Paritaprevir/Ritonavir + Dasabuvir are most frequently used in HCV genotype 1b Sofosbuvir + Ledipasvir are used in combination or Sofosbuvir is used alone (10).

There may be underlying dermatological diseases in hepatitis C patients, such as lichen planus, cryoglobulinemic vasculitis, that suggest hepatitis C infection. Such diseases may light the HCV diagnosis, while it is reported that the dermatological disease regresses with HCV treatment (11,12). Pruritus was reported to be 5.1-58.4% in hepatitis C patients (13-15). Pruritus is reported as the side effect of the DAA drugs used in the treatment of HCV (16,17). It is still a matter of discussion whether the pruritus arises from the HCV infection itself or the treatment (18). Direct-

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acting antivirals are safe drugs with a low side effect profile. The reported side effects of this Group of drugs are gastrointestinal side effects and pruritus (19). The safety and efficiency data regarding DAA drugs in chronic kidney disease (CKD) are not sufficient.

In this study, the demographical characteristics of the hepatitis C patients using DAA and the drug side effects, and the dermatological side effects and their management in the patients with CKD and renal transplantation, as well as hepatitis C patients using other DAA, were studied.

Methods

Study Design

This study was approved by the local ethics committee. A prospective study was conducted with adult chronic hepatitis C patients who used ObV/PTV/r + RBV, Sofosbuvir + Ledispavir, and Sofosbuvir and who supplied the drugs from our hospital. In our country, HCV drugs are distributed by certain designated pharmacies appointed by the government. The data of the patients who were diagnosed and had a drug report issued by more than 30 physicians and more than 10 sites, and who agreed to participate in the study was used. The patient data were obtained from the reports required to get the drug, and the study was completed with 200 HCV patients between February 2017 and March 2018.

These patients who were using OBV/PTV/r + RBV (Group 1, n=112), Sofosbuvir + Ledipasvir (Group 2, n=69) and Sofosbuvir (Group 3, n=19) were recorded in 3 separate Groups.

The patients' demographical characteristics, HCV genotype, the pattern of contamination, presence of cirrhosis in the liver, comorbidities, and the drugs used for them were questioned. All skin, hair, and mucosal examinations of the patients with regards to dermatological side effects were conducted before the treatment started and on the 1st month of the treatment. The patients who attended the visits at least three times were included in the study. A patient with any dermatological side effect was followed up throughout the treatment, and treatment was applied for the side effect that developed. The HCV contamination pattern, systemic comorbidities, Ribavirin use, and, if any, the previous treatments, previous dermatological diseases of the patients were questioned and recorded.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. The defining statistics are presented as numbers and percentages for categorical variables, and a mean, standard deviation (SD), and median are included for numeric variables. Comparison of numeric variables in two independent Groups was carried out using Student's t-test for normal distribution and the Mann-Whitney U test for non-normal distribution. The relationships between numeric variables were examined using the Pearson correlation analysis when parametric test conditions were met and the Spearmen correlation analysis when these conditions were not met. Statistical alpha significance level was assumed to be $p<0.05$.

Results

The female gender was dominant among 200 HCV patients in the study (n=113, 56.5%). The ages of the patients were between 19-92 years. (Avr: 59.2±13.7) While in most patients, the mode of contamination was unknown, dialysis was the second mode of contamination for HCV, followed by childbirth, surgeries, dental treatment, and one of the patients was contaminated by hair transplantation. Most of the patients were HCV genotype 1b (82%), and approximately 70% of the patients were firstly treated by DAA drugs.

Antiviral Treatment and Chronic HCV

One hundred twelve patients were using Group 1. 69 patients were using Group 2. 19 patients were using Group 3. 158 patients were non-cirrhotic, while eight patients were decompensated cirrhotic. 60% of the patients had comorbidities such as diabetes, coronary failure, asthma-COPD. Thirty-one patients had renal failure, and 17 of them underwent renal transplantation. Fourteen CKD patients were under dialysis treatment. Eight of CKD patients had pruritus (Table 1). In this study, 14 CKD patients had hemodialysis n=14, and 57% developed pruritus. While no side effects were observed in 2 patients who had liver transplantation, pruritus developed in 2 of 17 patients with renal transplantation, and others managed to complete the treatment without problems.

The great majority of the patients were using Group 1 drugs, and the most frequent side effect was pruritus. Almost all of the patients who developed pruritus were in this Group. The intensified pruritus in patients who previously had pruritus was recorded as a side effect. The patients whose pruritus was stable were not evaluated as a drug side effect. Pruritus regressed in many of the patients through symptomatic treatment. One of the patients developed nodular prurigo, and the lesions were regressed with topical corticosteroid ointment and antihistaminic tablets. When the patients who previously had xerosis were excluded, two patients had notable xerosis. The other concomitant dermatological diseases were at ratios similar to society. While pruritus was more prevalent in patients with diabetes mellitus (DM), hypertension (HT), and heart disease, the drug could be tolerated in those with no additional systemic comorbidities (Table 2).

Discussion

HCV is a ribonucleic acid virus from the Flaviviridae family with a single positive chain. As the virus is not entirely visualized, its structure is not clearly known, and its classification was made based on its genomic differences. Six genotypes (GT1-6), and each one was typed as several subgroups. The most frequent genotype 1 (GT1) and genotype 1a and genotype 1b subgroups are responsible for most GT1 infections worldwide (6,20). In our study, genotype 1b was the most frequent type, and this was compliant with the studies conducted in the same city and with the literature (4,6,21).

Hepatitis C patients may have some dermatological symptoms (12,15,22). and these are reported in the previous studies (12,23). Mix cryoglobulinemia, porphyria cutanea tarda, lichen planus, pruritus are among the diseases reported (17,24). The association of lichen planus and hepatitis C is being examined. Lichen patients were reported to be treated with DAA (25). In this study, no lichen disease was detected. The dermatological findings such as atopic eczema, psoriasis, acne rosacea, seborrheic dermatitis, and acne observed within the study scope were similar to society.

Pruritus is seen in chronic liver diseases and affects the quality of life (26). Although the cause of the pruritus development in such patients has not been yet determined, studies were conducted regarding the fibrosis in the liver, high enzyme levels, or bilirubin levels. Pruritus is also reported to have developed during the treatment of HCV patients (17,26,27).

DAA is effectively used in the treatment of HCV. In a recent review, the side effects of DAA were reviewed (28). In the studies conducted at advanced ages, it was found to be effective and reliable (29). In the study by Tachi et al. (30) it was reported that 10% of the patients had developed pruritus after DAA use, while some of the patients who had pruritus before treatment reported regression with the treatment. In this study, the pruritus ratio after DAA treatment resulted in 28%. This ratio was higher when compared to the literature. The reason for the

Table 1. Demographic characteristics of the patients, mode of contamination, concomitant systemic diseases, other systemic disease and ribavirin usage

		n%
Gender	Male	87 (43.5)
	Female	113 (56.5)
Age (years)	-	59.2±13.7 (19-92)
Disease time (year)	-	7.0±6.2 (0.5-35)
Diagnosis	Decompensated cirrhotic	8 (4.0)
	Compensated cirrhotic	34 (17.0)
	Cirrhotic	158 79.0
Contamitation type	Unknown	139 (69.5)
	Surgery	7 (3.5)
	Dialysis	41 (20.5)
	Child-birth	11 (5.5)
	Hair transplantation	1 (0.5)
	Drug-abuse	1 (0.5)
HCV Genotype	1a	18 (9.0)
	1b	164 (82.0)
	2	1 (0.5)
	3	5 (2.5)
	3a	11 (5.5)
	3b	1 (0.5)
Concomitant disease	Chronic renal failure	14 (7.0)
	Renal transplantation	17 (8.5)
	Liver transplantation	2 (1.0)
Other systemic disease	-	128 (64.0)
	HT	90 (45.0)
	DM	33 (16.5)
	COPD-ASTHMA	19 (9.5)
	CHF	2 (1)
	CAD	6 (3)
	Other	18 (9)
Ribavirin use	-	58 (29)
Treatment useage before	-	57 (28.5)

HT: Hypertension, DM: Diabetes mellitus COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, CAD: Coronary artery disease, HCV: Hepatitis C virus

Table 2. DAA usage Groups and skin side effects. Skin disease accompany to HCV patients

		n%
DAA	Group 1	112 (56)
	Group 2	69 (34.5)
	Group 3	19 (9.5)
Treated cures	-	2.7±1.2 (1-7)
Skin side effects	Pruritus	56 (28)
	Xerosis	2 (1)
	Conjunctivitis	1 (0.5)
Concomitant skin disease	Xerosis	11 (5.5)
	Dermatitis	13 (5.5)
	Psoriasis	6 (3.0)
	Pruritus	1 (0.5)
	Acne	1 (0.5)
	Atopic dermatitis	1 (0.5)
	Acne rosacea	1 (0.5)
	Vitiligo	1 (0.5)
	Seborrheic dermatitis	1 (0.5)

Group 1: Ombistavir/Paritaprevir/Ritonavir + Dasabuvir. Group 2: Sofosbuvir and ledispavir. Group 3: Sofosbuvir, DAA: Direct-acting antiviral drugs, HCV: Hepatitis C virus

different side effects reporting may be the patients failed to report due to mild progress or due to the humudity. The majority of the patients had comorbidities and the inclusion of CKD patients in the group, and the majority of the patients were 65 years or above. Most of the patients within the Group were 65 years or above. The ratio of pruritus development in patients who were under 65 years was 18.1%. Villani et al. (31) reported that pruritus, rash, and photosensitivity were slightly high in patients over 65 years of age. No examinations were made on the patients in our study. Therefore, no comments were made regarding the liver functions and bilirubin levels. There was no statistically significant difference between cirrhotic and non-cirrhotic groups.

Sofosbuvir was used alone in 19 patients and combination in 69 patients. Those who used this group of the drug did not develop pruritus (32).

In hemodialysis patients, the most frequent cause of the liver disease is HCV infection, and the anti-HCV ratio varies between 21.3 and 41.5. DAA was safely used in renal transplantation patients, and no side effects were observed in the patients (7,33). Although it was possible to observe systemic gastrointestinal side effects in CKD and renal transplantation patients, all patients managed to complete the DAA treatment (34). The authors reported that it is safe and relatively well tolerated in advanced renal failure and that no of-related specific toxicity was detected. The high ratio may be due to the absence of continuity in drug elimination in CKD patients. The side effects of renal transplantation patients matched the literature. The persistent pruritus following the skin moisturizing for xerosis in patients with renal failure and the pruritus regressed after discontinuing DAA were considered drug side effects.

Ribavirin was used as a supplement to the treatment (35). In the previous studies, it was reported that ribavirin might be a factor, and it has dermatological side effects by 10%, such as xerosis, alopecia, eczema, psoriasis (16,36). No difference was detected in terms of pruritus between the use of ribavirin or not.

Intravenous narcotic use is an essential mode of contamination for the virus infection. In our study, the use of narcotics was made through patient declaration. One patient continued using narcotics, and that he did not have dermatological side effects. No differences in dermatological side effects were detected between the patients experienced in terms of treatment and those using for the first time.

When asked about the drug's positive effect, almost all patients using DAA stated that they did not have flu. Since there is no pandemic during the study, and it is not included in planning at the beginning of the study, no clear data can be given. Data on the course of Coronavirus disease-2019 (COVID-19) patients in HCV patients using DAA may contribute to these drugs' COVID-19 effect. Currently, remdesivir has received fluorescein diacetate approval for COVID-19.

In dermatological side effects developed with DAA, the symptoms were minimized with good skincare, and the treatment was accomplished. Emollient creams, pomades with corticosteroid for short term use in patients with severe pruritus, and antihistamines were added to the treatment.

Study Limitations

The deficits of this study were the absence of liver function tests of the patients, and the viral charge at the beginning and the post-treatment efficiency were not evaluated. The correlation between treatment success and side effects was not evaluated.

Conclusions

Pruritus and skin rash are common with DAA drugs used in HCV treatment. Elderly patients with comorbidities such as DM and HT may be under at more risk, and pruritus complaints may be controlled with efficient skincare in such patients. The detailed examinations to be conducted in patients with pruritus and dermatological side effects may contribute to the explanation of the etiology.

Authorship Contributions

Concept: S.A., M.A., Design: S.A., M.A., Data Collection or Processing: S.A., M.A., Analysis or Interpretation: S.A., M.A., Literature Search: S.A., M.A., Writing: S.A., M.A.,

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Original Article

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Investigation of the Relationship Between IL-1Ra VNTR Variants and Psoriasis

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Abstract

Aim: Psoriasis is an inflammatory skin disease characterized by hyperproliferation of keratinocytes. The imbalance between Interleukin-1 (IL-1)/IL-1 receptor antagonist (IL-1Ra) is associated with increased pro-inflammatory cytokine production and the development of inflammatory disorders. The number of repeats in the polymorphic site where IL-1Ra has an 86 bp sequential repeat sequence is of functional importance as it includes possible binding sites for transcription factors. In this context, we aimed to investigate the relationship between psoriasis and IL-1Ra VNTR in Turkish society.

Methods: One hundred twenty one patients (79 female/42 male), 250 controls (142 women/108 male) were included in the study groups and genotyped by polymerase chain reaction-restriction fragment length polymorphism method. Genotype and allele distributions were examined between the patient and control groups. The gene counting method was used to calculate the allele frequencies.

Results: The A1 allele is excessive in the control group (p=0.001). In addition, the fact that all of our patients with psoriasis area and severity index <=10 were carriers of the A1 allele.

Conclusion: The A1 allele may have a protective effect in terms of the severity of the disease and the determination of IL-1 variants may be a guide in determining the treatment protocols of these patients.

Keywords: Interleukin-1, interleukin 1 receptor antagonist, single nucleotide polymorphism, psoriasis

Introduction

Psoriasis is an inflammatory skin disease that affects the skin, joints and tendons, characterized by keratinocyte hyperproliferation caused by T-cell mediated genetic with environmental factors (1-3). Although the altered production of inflammatory markers is assumed to play a key role in pathogenesis, the true scenario of psoriasis etiology is still unknown (4). The severity and progression of the disease vary in different patients. In different studies attending that these individual differences may arise from genetic susceptibility (5). Currently, more than 40 independent loci may play a predisposition role in psoriasis. Interleukin-1 receptor antagonist (IL-1Ra), an anti-inflammatory cytokine and is a member of IL-1 containing three related genes (IL-1α, IL-1β and IL-1RN) within a region of 430 kb on chromosome 2q14 (6). IL-1Ra which is binding to the IL-1 receptor and competitively blocks the effects of IL-1α and IL-1β. An imbalance between IL-1 and IL-1Ra is caused to the increasing pro-inflammatory cytokine production and the development of inflammatory disorders. The IL-1Ra gene has a penta-allelic polymorphic region which is containing variable numbers of a sequential repeat sequence of 86 bp in intron two (7). The number of repeats in the polymorphic area can can be important because of repeating sequence contains possible binding sites for transcription factors. There are various conflicting data according to the functional effect of these polymorphisms on IL-1α production. According to in vitro studies, the IL-1Ra A2 allele has been associated with increased IL-1Ra production in normal monocytes (8).

Several studies in various diseases including psoriasis, have shown a significant increase in the frequency of

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IL-1Ra A2 (9). IL-1Ra deficient mice have shown similar histological findings in human psoriasis (10,11). In addition, it has been reported increased IL-1Ra mRNA levels in cell cultures obtained from psoriasis patients and with this information relationship between the IL-1 gene complex and psoriasis is getting important so the researchers have focused their attention on the variations in this complex (12). Polymorphisms in *IL-1* gene complex are of considerable interest as they are thought to affect levels of IL-1 secretion.

However, studies which are investigating the relationship between IL-1Ra variable number of sequential repeats (VNTR) and psoriasis are quite limited and their results are conflicting. We aimed to investigate the relationship between psoriasis and IL-1Ra VNTR in Turkish population in this study.

Methods

Study Design

The present study protocol was approved by the Ethics Committee of the Giresun University Faculty of Medicine (number: KAEK-115) and written informed consents were obtained from all patients. All procedures performed in this study were in compliance with the ethical standards of the institutional and/or national research committee and the Declaration of Helsinki (13). In this study, 121 psoriasis patients who applied to Giresun University. Ilhan Ozdemir Training and Research Hospital between 2019-2020, diagnosed clinically or histopathologically, were included in our study group. As the control group, 250 individuals who applied to the dermatology outpatient clinic with a dermatological disease and were age-matched were included in the study group. These individuals had no history of psoriasis or any chronic inflammatory disease. The demographic and clinical characteristics of both psoriasis patients and the control group were recorded in synchronized Excel files for later use. Psoriatic arthritis was investigated in all patients. Children (age <18) (n=5), pregnant and lactating participants (n=2), and participants (n=10) with a history of any immunological or inflammatory disease were excluded from the study.

Interleukin-1 Receptor Antagonist Genotype Analysis

We isolated genomic DNA from the leukocytes using Roche isolation kit (Roche high pure isolation kit, Germany). The extracted DNA was maintained at 4 °C until analysis. The VNTR mutation in the IL-1Ra gene was determined by polymerase chain reaction (PCR). The PCR product was generated by the use of oligonukleotid F: 5 "-CTCAGCAACACTCCTAT-3" R: 5 "-TCCTGGTCTGCAGGTAA-3". PCR protocol for the polymorphic region within intron 2 of the *IL-1Ra* gene with a VNTR of 86 bp; initial denaturation at 95 °C for 5 min, followed by 35 cycles of 95 °C for 45 s, 55 °C for 45 s and 72 °C for 45 s before terminal elongation at 72 °C for 10 min. The obtained PCR products were genotyped by imaging under UV in a 2% agarose gel and five alleles were characterized according to the number of repeats (14). Allele 1 (four repeats) was 410 bp, allele 2 (two repeats) 240 bp, allele 3 (five repeats) 500 bp, allele 4 (three repeats) was 325 bp, and allele 5 (six repeats) was 595 bp.

Statistical Analysis

The statistical analysis of this study was made using the SPSS 20 package program. Statistical significance was taken as $p<0.05$. Alleles and genotype frequencies were calculated by direct counting. The chi-square (χ^2) test was used to evaluate the intergroup differences in the frequency of genotype and alleles. Odds ratio (OR) and 95% confidence interval (95% CI) are given to determine the risk factor between groups.

Results

The demographic characteristics of the study groups are given in Table 1. The patients were divided into two groups according to the age of onset of psoriasis [<=40: early onset (n=78); >40: late onset (n=43)]. Among our patients, 92 people had no psoriatic arthritis, while 29 suffered from psoriatic arthritis. In addition, 101 patients did not have a family history of psoriasis, while 20 patients had a history of psoriasis in their first-degree relatives.

In the patient and control groups included in the study, only 3 alleles [A1=410 (four replicates), A2=242 (two replicates), A3=500 (five replicates)] were observed (Table

Table 1. Demographical characteristics of the study population

		Cases (n=121)	Controls (n=250)	p
Age (Years)	(Mean ± SD)	44.08±14.17	47.61±12.0	NS
Sex n (%)				
Male Female	-	42 (34.7%) 79 (65.3%)	108 (43.2%) 142 (56.8%)	NS
Artrit n (%)				
Artrit + Artrit -	-	29 (24.0%) 92 (76.0%)	- -	-
Age of onset n (%)	<=40 >40	78 (65.0%) 43 (35.0%)	-	-
Family history n (%)	+ -	20 (16.5%) 101 (83.4%)	-	-
PASI n (%)	>10 <=10	108 (89.3%) 13 (10.7%)	-	-

Mean values were compared between patients and controls by using the Student's t-test. Qualitative data were analyzed by the chi-square test. NS: Not significant, PASI: Psoriasis area and severity index, Data are presented as mean ± SD and n (%). Bold values were statistically significant ($p<0.05$). n: Number of samples SD: Standard deviation

2). The frequency distribution of these alleles in Turks is similar to other world populations, A1 is the most common allele, followed by A2 and A3 are rare alleles. There was a statistically significant difference in genotype and allele frequencies between patients and controls (p<0.001). The IL-Ra VNTR allele and genotype frequencies in psoriasis patients and controls are shown in Table 2. The A1 allele was present at a significantly higher frequency in the control group (p=0.001, OR: 0.322% 95 Cl: 0.159-0.655). In addition, interestingly, all of our patients with Psoriasis area and severity index (PASI) <=10 are carriers of the A1 allele (data not shown). The A2 and A3 allele did not show a significant difference between the two groups (p=0.363; p=0.560, respectively).

Discussion

Two important studies in 2014 and 2019 highlighted the importance of the IL-1β-IL-1R signaling pathway in psoriasis. In one of these studies Lowes et al. (3) showed IL-1β-IL-1R signaling pathway plays critical roles in psoriasis pathogenesis and in the other Cai et al. (15) data showed that the IL-1β-IL-1R signaling pathway is associated with disease progression and treatment response. The results of these two studies suggest that this pathway not only a target for the treatment of the disease,it also for a an important target in disease progression and response of treatment.

Di Paolo et al. (16) demonstrated the effects of IL-1Ra on blocking IL-1α and IL-1β activity. In addition, IL-1Ra knockout mice developed skin inflammation with histopathological characteristics similar to human psoriasis (17), while positive effects were observed in individuals with psoriasis treated with recombinant IL-1Ra (18). The significantly higher mRNA expressions of IL-1 receptor antagonists evaluated in peripheral blood mononuclear cells (PBMCs) of 10 psoriatic patients and six healthy controls in psoriasis patients also a documentation of the relationship between the IL-1 family and psoriasis (12). When this information is evaluated and the role of IL-1Ra in controlling inflammation is considered, it can be assumed that the variations in this gene may contribute to the pathogenesis of psoriasis by affecting gene expression levels. Studies showing that the IL-1Ra VNTR A2 allele is associated with a variety of epithelial-related chronic inflammatory diseases, including alopecia areata, lichen sclerosis, systemic lupus erythematosus, ulcerative colitis and scleroderma (19,20). A few studies which are investigating the relationship between psoriasis and IL-1Ra, are very limited and contain conflicting results.

One of study from the G.Britain by Tarlow et al. (9) showed that the frequency of the A2 allele increased in the early-onset (<40 years) cohort with psoriasis and decreased significantly in the late-onset (>40 years) cohort compared to controls, and on the other hand Moorchung et al. (21) reported that there is no relationship between VNTR and psoriasis.

In addition; other studies from Egypt, Taiwan, and Canada showed that there was no significant difference in the frequencies of all genotypes and alleles related to the IL-1Ra VNTR polymorphism (22-24). Finally, a meta analysis result emphasized that there is no relationship between IL-1Ra and Psoriasis pathogenesis (25).

In the results of our study, the A1 allele was found to be statistically significantly higher in the control group compared to the patient group. This suggests that the A1 allele may have a protective effect against the severity of the disease. In addition, the fact that all of our patients with PASI <=10 were carriers of the A1 allele also supports this finding. A2 and A3 alleles did not show statistically significant differences in patient and control groups, consistent with the studies from Egypt, Taiwan, and Canada.

Table 2. Genotype and allele distributions in study groups

Genotip								
	A1/A1		**A1/A2**	**A1/A3**		**A2/A2**		**A3/A3**
Cases n (%) (n=121)	50 (41.3%)		42 (34.7%)	7 (5.8%)		10 (8.3%)		10 (8.3%)
Controls n (%) (n=250)	117 (46.8%)		109 (43.6%)	11 (4.4%)		13 (5.2%)		0 (0.0%)
p	<0.001*							
Allele								
	A1 (+)	A1 (-)	A2 (+)	A2 (-)	A3 (+)	A3 (-)	A4 (+)	A5 (+)
Cases (n=121)	0.83	0.16	0.43	0.57	0.05	0.95	0.0	0.0
Controls (n=250)	0.94	0.06	0.48	0.52	0.04	0.96	0.0	0.0
X^2	10.579		0.828		0.339		-	-
p	0.001**		0.8363		0.560		-	-

Data are presented as n (%). Bold values were statistically significant (p<0.05). n: Number of samples
*: X^2 test (two degrees of freedom)
**: X^2 test (one degree of freedom)

Study Limitations

Our study has some limitations because of IL-1Ra serum levels and expression levels could not compared. Therefore, we think that our study should be supported by new studies which have expression levels in a larger sample group.

Conclusion

Our study is the first study which was investigating psoriasis and IL-1Ra VNTR polymorphism in Turkish population. As a result; we think that the A1 allele may have a protective effect in terms of the severity of the disease and the determination of IL-1Ra variants may be a guide in determining the treatment protocols for these patients.

Authorship Contributions

Concept: A.B.A.T., Design: A.B.A.T., B.A., Data Collection or Processing: A.B.A.T., B.A., Analysis or Interpretation: A.B.A.T., B.A., Literature Search: A.B.A.T., B.A., Writing: A.B.A.T.

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Original Article

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Evaluation of Dermatology Consultations in Internal Medicine Wards: An Analysis of 510 Cases from A Tertiary Center

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Abstract

Aim: To evaluate the reasons for dermatology consultations in hospitalized patients in the internal medicine services and the treatments recommended based on these consultations.

Methods: The data of patients who were hospitalized in the internal medicine services between June 2018 and June 2020 were evaluated retrospectively including patients' demographics, reasons for the consultation, recommended additional tests and treatments by the dermatologist.

Results: A total of 510 patients (8.6%) (51% male, 49% female, mean age 67.3±16.0 years) requested dermatology consultations were reviewed among patients hospitalized in internal medicine services. The most common reason for the dermatology consultation was cutaneous and subcutaneous infections (n=156, 30.6%) followed by decubitus ulcer (n=94, 18.4%) and vascular diseases (n=50, 9.8%). Topical and/or systemic treatments were recommended to 87.1% of the patients. Duration of hospitalization was longer in patients who requested dermatology consultations than patients not requested (p<0.001).

Conclusion: Infectious causes and decubitus ulcer were the two most common reasons for dermatology consultations. Dermatology consultations are of great importance in hospitalized patients to decrease morbidity and the duration of hospitalization.

Keywords: Dermatology, consultation, internal medicine, decubitus ulcer

Introduction

Dermatology consultations requested from hospitalized patients, particularly in the internal medicine services, are of great importance for the diagnosis of the emerging skin manifestations, giving a clue about any accompanying systemic diseases and management of the disease (1). Dermatological problems are common in hospitalized patients and it is an important cause of morbidity (2).

There are various studies available in the literature evaluating the dermatology consultations (1-11). According to these studies, 21.5% to 45% of the dermatology consultations were requested from the internal medicine services, following emergency, pediatrics, surgery services. Additionally, cutaneous, subcutaneous infections, inflammatory skin diseases and drug eruptions were reported as the most common reasons for requesting a dermatology consultation in these studies. However, there are not many studies evaluating the reasons for requesting dermatology consultations focusing only on the hospitalized patients in internal medicine services (1). Determining the dermatological findings in hospitalized patients in internal medicine services may result with a decreased morbidity and a shorter duration of hospitalization.

Hence, the aim of this study is to retrospectively evaluate the dermatology consultations requested from patients hospitalized in the internal medicine services, and to scrutinize the reasons for requesting dermatology consultations, the diagnostic tests carried out and the recommended treatments for dermatological disorder.

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Methods

Study Design

Dermatology consultations of the patients hospitalized in the internal medicine service of University of Health Sciences Turkey Haseki Training and Research Hospital between June 2018 and June 2020 were retrospectively analyzed based on their electronic database records. All these patients had been assessed by one of the dermatology specialists that work in our unit and who was on duty at the relevant date. The demographic characteristics of the patients, the reasons for the dermatology consultation requests, dermatological diagnoses, and the diagnostic tests recommended and implemented, and the recommended dermatological treatments were recorded. The ethics committee approval (number: 208/040620) of our study was obtained from the University of Health Sciences Turkey Haseki Training and Research Hospital Local Ethics Committee.

Dermatological Assessment

Dermatological diagnoses were categorized into eight main groups, namely, "cutaneous or subcutaneous infections", "inflammatory skin conditions", "drug eruptions", "autoimmune and bullous skin diseases", "skin manifestations of systemic diseases", "skin tumors", "vascular-related skin diseases" and "other" (if a diagnosis cannot be categorized under any of the foregoing groups). Additionally, other data such as the number of recurrent consultations and duration of the hospitalization regarding each patient were evaluated.

Statistical Analysis

The research data were worked up into Excel sheets. Statistical analyses were carried out using the Statistical Package for the Social Sciences Version 15.0 for Windows software. Descriptive statistics with regards to numerical variables were reported as mean, standard deviation, minimum and maximum values. The categorized groups were compared using the chi-square test. A statistical significance level of alpha was accepted as $p<0.05$. In the event that the comparison between the mean values of any two groups has resulted in a p (probability) value less than 0.05 indicating a statistically significant difference, the associated effect size was also calculated using the "Cohen's d" index in order to comprehend the level of any such statistically significant difference.

Results

One or more dermatology consultations were requested for the 510 (8.6%) patients among 5957 patients hospitalized in the internal medicine services of our hospital between June 2018 and June 2020. The demographic characteristics of these patients are given in Table 1. The mean age of these patients was 67.3±16.0 years. Of these patients, 260 (51%) were male and 250 (49%) were female. Cutaneous or subcutaneous infections were the most common reason (n=156, 30.6%) for requesting a dermatology consultation, with fungal infections (15.9%) being the most common type of cutaneous infection registered within this group. The second most common reason for requesting a dermatology consultation was decubitus ulcer (n=94, 18.4%), followed by vascular diseases (n=50, 9.8%) and inflammatory skin diseases (n=45, 8.8%) (Table 2, Figure 1). Decubitus ulcers and vascular conditions were more common in patients ≥50 years-old (p=0.008, p=0.021, respectively), whereas autoimmune bullous diseases were more common in patients <50 years-old (p=0.023, respectively) (Table 3).

Additional tests were required in 48.2% of these patients in order to confirm the dermatological diagnoses. The most common performed additional tests were as follows; direct fungus examination (n=110), Wood's lamp examination (n=49), skin punch biopsy (n=30), bacterial culture (n=28) and pathergy test (n=25) (Figure 2).

Topical treatments were recommended in 387 (87.1%) of the patients for their dermatological disorders, either alone or in addition to any systemic therapy. Recommended topical treatments were as follows; topical antifungals (28.2%), topical epithelizers (26.1%), topical antibiotics (20.2%), topical steroids (19.4%), and wound dressings (15.9%). A systemic treatment was recommended in 110 (21.6%) patients, whereas no additional treatment was recommended in 66 (12.9%) patients. Additionally, in 70 (13.7%) patients, the respective findings revealed the need for seeking consultation from other specialties.

Table 1. Demographic characteristics of the patients for whom a dermatology consultation was carried out

		n
Patients for whom a dermatology consultation was requested		510/5.957 (8.6%)
Gender	**Female**	250 (49%)
	Male	260 (51%)
Age mean ± SD (minimum-maximum)		67.3±16.0 (20-100)
Distribution by age groups	20-29	12 (2.4%)
	30-39	18 (3.5%)
	40-49	47 (9.2%)
	50-59	79 (15.5%)
	60-69	105 (20.6%)
	70-79	115 (22.5%)
	80-89	115 (22.5%)
	90-100	19 (3.7%)

SD: Standard deviation

Table 2. Dermatological diagnoses established by dermatology consultation		
	n	%
Cutaneous/subcutaneous infections	**156**	**30.6**
Dermatophytosis	30	5.9
Candidiasis	29	5.7
Cellulitis	23	4.5
Onychomycosis	13	2.5
Secondary infection	13	2.5
Herpes zoster	8	1.6
Herpes simplex	6	1.2
Intertrigo	6	1.2
Folliculitis/furuncles	5	1.0
Scabies	5	1.0
Pyoderma	4	0.8
Pityriasis versicolor	3	0.6
Impetigo	3	0.6
Lymphangitis	2	0.4
Pediculosis	1	0.2
Viral exanthema	1	0.2
Ecthyma	1	0.2
Orf	1	0.2
Abcess	1	0.2
Erysipelas	1	0.2
Drug eruptions	**27**	**5.3**
Drug eruption (maculopapular, acneiform, lichenoid drug eruption)	19	3.7
Drug induced ulcer	5	1.0
Stevens-Johnson syndrome	3	0.6
Inflammatory skin diseases	**45**	**8.8**
Contact dermatitis	9	1.8
Psoriasis	6	1.2
Erythema nodosum	6	1.2
Piyoderma gangrenozum	4	0.8
Nummuler dermatitis	4	0.8
Diaper dermatitis	4	0.8
Urticaria	3	0.6
Seborrheic dermatitis	3	0.6
Rosacea	2	0.4
Lichen planus	1	0.2
Angioedema	1	0.2
Ichthyosis	1	0.2
Hidradenitis suppurativa	1	0.2
Vascular pathologies	**50**	**9.8**
Stasis dermatitis	28	5.5
Vasculitis	7	1.4
Ecchymosis	6	1.2
Acrocyanosis	2	0.4
Vascular malformation (hemangioma, venous lacquer)	2	0.4
Petechiae-purpura	2	0.4
Thrombophlebitis	2	0.4
Chronic lymphedema	1	0.2
Autoimmune and bullous diseases	**16**	**3.1**
Bullous pemphigoid	7	1.3
Linear IgA bullous dermatosis	1	0.2
Bullous systemic lupus erythematosus	1	0.2
Acquired epidermolysis bullosa	1	0.2
Skin tumors	**16**	**3.1**
Benign neoplasm of skin	8	1.6
Cutaneous T-cell lymphoma	4	0.8
Basal cell carcinoma	2	0.4
Cutaneous metastasis	1	0.2
Kaposi's sarcoma	1	0.2
Skin manifestations of systemic diseases	**23**	**4.5**
Diabetic foot	16	3.1
Uremic pruritus	4	0.8
Diabetic dermatopathy	1	0.2
Eruptive xanthoma	1	0.2
Sclerodactyly	1	0.2
Other (unclassified)	**197**	**38.6**
Decubitus ulcer	94	18.4
Pruritus	31	6.1
Callus	10	5.1
Keloid	6	1.2
Artificial dermatosis	6	1.2
Prurigo nodularis	3	0.6
Perforating dermatosis	3	0.6
Other (terra-firma forme dermatosis, postlesionel pigmentation, chloasma etc.)	44	8.6

It was also recommended to evaluate some patients (n=8, 1.6%) in terms of malignancies, which may associate with the dermatological disorder.

A single dermatology consultation was deemed to be sufficient in 87.3% of the patients, whereas in 65 (12.7%) patients recurrent consultations were required. The reasons indicated for requesting a recurrent consultation were as follows; newly developed dermatological problems (n=30, 5.9%), unresponsiveness to the treatment recommended in the previous consultation (n=22, 4.3%), and follow-up of the dermatological condition (n=13, 2.5%).

While the mean duration of hospitalization of patients, requested a dermatology consultation was 6.72±6.86 days (median: 5 days, range: 1-48 days); it was 4.27±4.85 days (median: 3 days, range: 1-62 days) for whom no dermatology consultation was requested. There was a statistically significant difference between these two

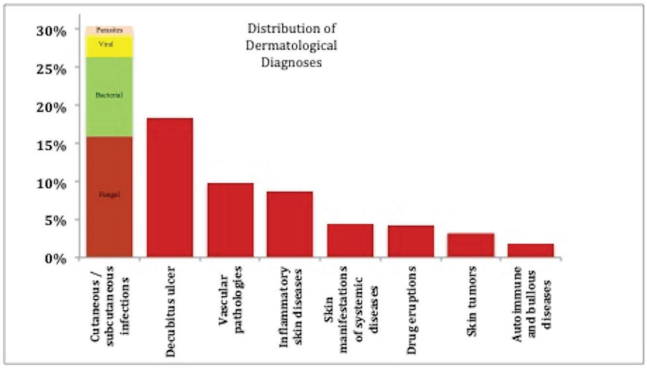

Figure 1. Distribution of dermatological diagnoses

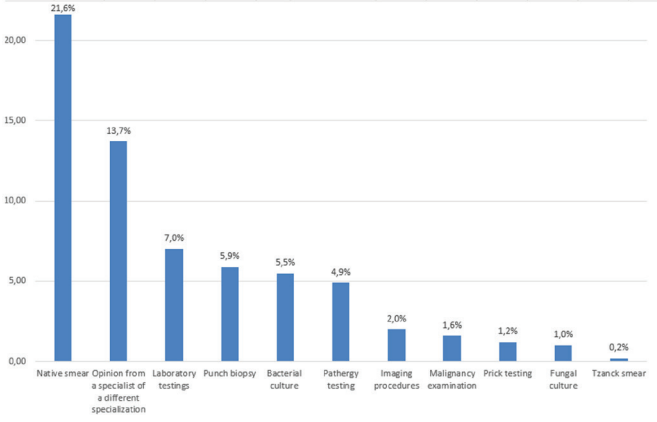

Figure 2. The proportion of each additional test and/or referrals based on the total of tests and/or referrals requested

Table 3. Distribution of diseases seen in patients over and below the age of 50

	Age				
	<50 years		≥50 years		
	n	%	n	%	p
Cutaneous/subcutaneous infections	22	28.6	134	30.9	0.677
Drug eruptions	3	3.9	24	5.5	0.783
Inflammatory skin diseases	9	9.1	36	7.4	0.605
Vascular pathologies	2	2.6	48	11.1	0.021
Autoimmune and bullous diseases	6	7.8	10	2.3	0.023
Skin tumors	1	1.3	15	3.5	0.487
Decubitus ulcer	7	9	87	20.1	0.008
Skin manifestations of systemic diseases	4	5.2	19	4.4	0.765

groups in terms of the mean duration of hospitalization ($p<0.001$). Cohen's d effect size analysis value was calculated as 0.48, revealing an effect size that is between medium effect (0.5) and small effect (0.2), and is thus considered significant.

Discussion

In this study, the dermatology consultations requested for patients hospitalized in the internal medicine service of a tertiary health center were reviewed in terms of the reasons for requesting a dermatology consultation and the treatments recommended based on these consultations.

Among the patients hospitalized in the internal medicine service, a dermatology consultation was requested for 510 patients (8.6%). The most common reasons indicated for the dermatology consultations requested for these patients were cutaneous and subcutaneous infections, representing 30.6% (n=156) of them. Decubitus ulcer (n=94, 18.4%) was the second most common reason for requesting a dermatology consultation, which was followed by vascular pathologies (n=50, 9.8%) including stasis dermatitis as the most commonly observed type of vascular pathology, and inflammatory skin diseases (n=45, 8.8%).

Similar to the results of our study, the most common reasons for requesting a dermatology consultation reported in the literature were infectious causes (18.5% and 29.8%) and inflammatory diseases (16.6% and 33.1%) (7,8). On the other hand, Lorente-Lavirgen et al. (10) reported inflammatory diseases (36.2%) as the most common reason for requesting a dermatology consultation, followed by autoimmune diseases. This result may be due to the fact that the mean age of the patients included in the study of Lorente-Lavirgen et al. (10) was around 50 and that their hospital contains a globally accepted rheumatology unit.

In terms of etiological agents, it was observed that more than half of the infectious causes (n=81) were skin fungal infections. Similar to the results of our study, Mancusi and Festa Neto (11) also reported that fungal infections accounted for nearly half of the infectious causes. On the other hand, there are also studies in which bacterial agents were reported as the most common infectious cause in the literature (4).

The fact that 85% of our patients were over the age of 50 and 70% of them were over the age of 65 which may be the reason for the relatively higher frequency of fungal infections found in our study. A relatively higher frequency of vascular skin pathologies (mainly stasis dermatitis), the third most common reason (9.8%) for requesting a among dermatology consultations in our study, may also be attributed to the same reason. Similarly, Storan et al. (8) and Mancusi and Festa Neto (11) reported that stasis dermatitis and vascular pathologies were seen in 7.3% and 5% of the patients, respectively.

Distribution of the dermatology consultations regarding age revealed that decubitus ulcers and vascular conditions were more common in patients ≥50 years-old (p=0.008, p=0.021, respectively), whereas autoimmune bullous diseases were more common in patients <50 years old (p=0.023, respectively). These results are compatible with the results reported in comparable studies (12-14).

Additional medical workup including Tzanck smear, Wood's lamp examination, skin punch biopsy, ie; may be required at the diagnosis of the dermatological diseases in patients requested consultations. Additional medical workup was requested in 48.2% of the patients included in our study, and this ratio is compatible with similar studies ranging from 6.4% to 48% (3,5,11). However, certain tests specific to the field of dermatology such as the patch test, were not included in the requested medical workup, as it is recommended in our hospital to be performed under elective conditions following the discharge of the patient from the internal medicine service.

In our study, skin tumor diagnosis was made in 3.1% of the patients for whom a dermatology consultation was requested. Among these patients, 4 patients had cutaneous T-cell lymphoma, 2 patients had basal cell carcinoma, 1 patient had cutaneous metastasis, and 1 patient had Kaposi's sarcoma. In comparison, Tay et al. (7) reported neoplasia in 4.8% of the patients, whereas Mancusi and Festa Neto (11) reported benign and malignant neoplasia in 6.7% of the patients.

Number of recurrent consultations requests has also been discussed in the literature as an indirect indicator of whether the dermatological problem is remedied or not. Fischer et al. (4) (reported that a single dermatology consultation was sufficient in 85% of the cases, compared to 71.8% and 60.9% of the cases in the studies of Penate et al. (5) and Connolly and Silverstein (3), respectively. Similarly, in our study, a single consultation was deemed to be sufficient in 87.3% of the cases. In terms of treatments recommended within the scope of dermatology consultations; Connolly and Silverstein (3) reported that topical treatments were recommended to 80.1% of the patients, and that systemic treatments were recommended to 19.1% of the patients (3). In comparison, in our study, topical treatments were recommended to 87.1% of the patients either alone or in addition to a systemic treatment. In the light of these data, it can be concluded that a single dermatology consultation is usually enough to resolve dermatological conditions and recurrent dermatology consultations are rarely needed, and topical treatments are often sufficient for these patients.

In our study, the duration of hospitalization was found to be significantly longer in patients, for whom a dermatology consultation was requested, compared to other patients. Similarly, it was stated in the study conducted by Philips et al. (9) that the median duration of hospitalization was 11 days in patients for whom a dermatology consultation was requested, compared to only 5 days in patients, for whom a dermatology consultation was not needed (p=0.001). This result suggests that the rate of elective consultation requests, particularly for reasons of fungal infections, may increase as the duration of hospitalization get longer. Another reason for the significantly longer duration of hospitalization in patients for whom a dermatology consultation was requested may be that dermatological findings are cross-examined in patients with longer hospitalizations in order to have a clue in the underlying diseases, and symptoms such as decubitus ulcer and drug eruptions may emerge in patients with longer duration of hospitalization.

Study Limitations

An important limitation of this study is that it was based on hospital data system records and carried out retrospectively. In addition, there was not any data about the period between the time of emergence of the dermatological condition and the time of requesting the dermatology consultation, as well as about the correlation between the pre-diagnosis made by the internal medicine physician and the diagnosis made by a dermatologist. Another limitation of our study was not including the data of dermatology consultations requested from subspecialties of internal medicine of our hospital. In addition patients requested consultations were evaluated by various dermatologists which may result in to a challenge for diagnosis in this respect.

Conclusion

It was found that infectious causes and decubitus ulcers constitute a major part of the reasons for requesting dermatology consultations in patients hospitalized in the internal medicine service, and it has been established that dermatology consultations are of great importance in resolving problems associated with dermatological conditions diagnosed during hospitalization, such as prolonged hospitalization, additional economic costs and workforce loss. Therefore, it is recommended to provide trainings for the internal medicine and dermatology residents on the diagnosis and management of these diseases and for the nurses and auxiliary healthcare personnel working in the internal medicine service team on the preventive measures, especially with respect to decubitus ulcers.

Authorship Contributions

Concept: T.O.A., H.S., F.T., Design: T.O.A., T.A., Data Collection or Processing: H.S., F.T., Analysis or Interpretation: T.O.A., T.A., Literature Search: T.O.A., Writing: T.O.A.

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The Relationship of Hepatits B Core Antibody Positivity with Demographic and Laboratory Parameters in Hemodialysis Patients

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Abstract

Aim: The presence of hepatitis B core antibody (HBcAb) is an indication of exposure to hepatitis B virus infection. We aimed to investigate the rates of positive HBcAb and its' association with demographical and laboratory parameters among patients undergoing hemodialysis.

Methods: Patients were divided into two groups as HBcAb positive and HBcAb negative. This study was conducted at a training and research hospital over 3 months period between October and December 2020. Demographical data and laboratory results were recruited from most recent medical records.

Results: A sum of 237 patients on hemodialysis were enrolled in the study. Fifty nine patients (25%) were HBcAb positive and 178 patients (75%) were HBcAb negative. Statistically significant difference was found between groups in terms of anti-HBs positivity (96.6% vs 79.2%; p=0.002), diabetes mellitus (DM) prevalence (32% vs 19%; p=0.036) and white blood cell count (WBC) levels (7.7±2.5 x10^3/µL vs 7.1±2.1 x10^3/µL; p=0.044). In linear regression analysis (variables: age, HBsAb, WBC and DM) HBcAb was found independently associated with age (t: 3.139; p=0.002), HBsAb (t: 3.998; p<0.001), WBC (t: 2.166; p=0.031) and DM (t: 2.749; p=0.006).

Conclusion: We found high rates of positive HBcAb. Positive HBcAb should be taken into account in immune-compromised patients such as dialysis patients.

Keywords: Hepatitis B virus, hepatitis B antibodies, hepatitis B core antigens, hemodialysis

Introduction

Patients on hemodialysis are under increased risk for hepatitis B virus (HBV) infection (1,2). The incidence of hepatitis B infection was about 0.12% in patients undergoing dialysis in the United States in 2002 (3). The incidence of HBV infection in dialysis differ worldwide according to the endemicity at in that region (4). The presence of hepatitis B core antibody (HBcAb) is an indication of exposure to HBV infection. In patients with HBcAb positive, when HBsAg is negative, HBV-DNA testing is not performed because these patients are not considered to be infectious. In case of receiving immune suppressive treatment, immune-suppressed patients such as hemodialysis patients with positive HBcAb, must receive prophylactic antiviral therapy against hepatitis B reactivation. Despite high antibody titers, reactivation of HBV infection has been shown in the literature after immunosuppressive therapy in HBcAb positive patients (5). Another important issue related to positive HBcAb is occult hepatitis B infection (OBI) which occurs as the result of mutations at the genes those encode surface antigen of HBV (6). Two subgroups of OBI according to the presence of serological markers had been described. If only HBV-DNA is positive whereas both HBsAg and HBcAb are negative, this situation is called seronegative OBI. On the other hand, if HBV-DNA is positive with the seropositivity of either HBcAb and HBsAg together or with the seropositivity of HBcAb alone, this situation is

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called seropositive OBI. In both types, common laboratory finding is the positivity of HBV-DNA (7). In the literature, it was shown that the incidence of seronegative OBI is about 20% of all OBI cases (8). After the routine clinical use of the HBsAg test, there has been a serious decrease in HBV infection rates. However, testing for HBsAg solely is not sufficient to detect OBI cases. The clinical significance of OBI is based on its possible clinical consequences. The undetected and untreated OBI may result with hepatocellular complications including carcinoma and cirrhosis (9). In addition, if OBI cases are not properly isolated, HBV infection can be transmitted in dialysis units.

In the present study, we investigated the rates of positive HBcAb and its' association with demographical data and laboratory parameters among patients undergoing hemodialysis in our cohort.

Methods

Study Design

The study was approved by institutional ethics committee of Izmir Bozyaka Training and Research Hospital at the (number; 4, date: 28.10.2020). This study was conducted at a training and research hospital and its satellite dialysis units over 3 months period between October and December 2020. The study included hemodialysis patients who were older than 18 years old. All patients were enrolled in the study after providing written informed consent. Patients with overt HBV infection with positive HBsAg and HBV-DNA were excluded. The patients included in the study were divided into two groups according to the presence of IgG type HBcAb positivity.

Laboratory Assessment

The plasma samples were obtained during monthly periodic visits of hemodialysis patients enrolled in the study. The serological markers of HBV, hepatitis C virus (HCV) and human immunodeficiency virus (HIV) were determined via ELISA (Access and Bio Rad, Beckman-Coulter, California, USA) kits. HBV-DNA and HCV-RNA were measured by polymerase chain reaction (PCR) technique with the manufacturers Artus GmbH HBV RG PCR kit, Hamburg, Germany and Cobas Amplicor HCV Monitor test, version 2.0 kit, Roche Diagnostic Systems, California, USA, respectively. The information about the vaccination and the history of blood transfusion of each patients was obtained from medical records. Arrangement of the normal limits of alanine and aspartate aminotransferases were done according to the data in the literature (10). Demographical data such as age and gender, laboratory data such as complete blood count results, albumin levels, haemoglobin A1c levels [in patients with diabetes mellitus (DM)], kt/V and urea reduction ratio (URR) results were obtained from most recent medical records.

Statistical Analysis

Categorical variables those were compared using the chi-square test and Fischer's Exact test, were reported as number and percentages. Besides, continuous parametric variables those were compared using Student's t-test, were reported as means ± standard deviation. Mann-Whitney U test was used to compare parameters not showing normal distribution such as aspartate transaminase (AST), alanine aminotransferase (ALT), time of last vaccination and antibody titers. Linear regression analysis was made for HBcAb. In linear regression analysis of HBcAb variables were age, HBsAb, WBC and DM. The comparison was made using the Enter method. SPSS18.0 (Chicago, IL USA) was used in performing statistical analysis. The threshold value in terms of statistical significance was $p<0.05$.

Results

A sum of 237 hemodialysis patients were enrolled in the study. Fifty-nine patients (25%) were HBcAb positive and 178 patients (75%) were HBcAb negative. Twenty patients (34%) in HBcAb positive patients and 76 patients (43%) in HBcAb negative patients were female. There was no statistically significant difference between HBcAb positive and HBcAb negative patients in terms of gender [34/66 female (F)/male (M) (%) vs 43/57 F/M (%); p=0.23]. There was statistically significant difference between HBcAb positive and HBcAb negative patients in terms of age (64±11 vs 60±15; p=0.018), respectively. There were 2 patients (0.8%) with isolated positive HBcAb. HBV-DNA results were negative in HBcAb positive patients including either isolated HBcAb or in patients with positive HBcAb and/or HBsAb. Demographical and laboratory results of HBcAb positive and HBcAb negative patients are presented in Table 1. The distribution of patients in HBcAb positive and HBcAb negative patients in terms of gender is presented in Figure 1.

HBsAb was positive in 57 of 59 patients in HBcAb positive patients; 141 of 178 patients in HBcAb negative patients and there was statistically significant difference between HBcAb positive and HBcAb negative patients in terms of HBsAb positivity (96.6% vs 79.2%; p=0.002), respectively. In terms of HBsAb titers, there was no significant difference between HBcAb positive and HBcAb negative patients [196.6 (469.1) mIU/mL vs 136.2 (425.6) mIU/mL; p=0.111]. There was statistically significant difference between HBcAb positive and HBcAb negative patients in terms of the mean time of last vaccination [12 (30) months vs 5 (17) months; p=0.012], respectively.

Type-2 DM was in 19 of 59 patients in HBcAb positive patients and 34 of 178 patients in HBcAb negative patients

and there was statistically significant difference between groups (32% vs 19%; p=0.036), respectively. The history of blood transfusion was in 11 of 59 patients in HBcAb positive patients and 27 of 178 patients in HBcAb negative patients and there was no statistically significant difference between groups (19% vs 15%; p=0.528). In terms of dialysis sufficiency, there was no statistically significant difference between HBcAb positive and HBcAb negative patients in terms of kt/V (1.5±0.3 vs 1.6±0.4; p=0.104) and URR (71±7% vs 72±8%; p=0.490), respectively.

In terms of laboratory parameters that we evaluated between HBcAb positive and HBcAb negative patients, although the results were close, there was statistically significant difference in terms of WBC levels (7.7±2.5 x103/μL vs 7.1±2.1 x103/μL; p=0.044). There were 3 patients with positive anti-HCV. None of them were with positive HBcAb and HBsAb. Also, HCV-RNA was found negative for each individual as well. Variables those found significantly associated with HBcAb were assessed in linear regression analysis (variables: age, HBsAb, WBC and DM). HBcAb was found independently associated with age (t: 3.139; p=0.002), HBsAb (t: 3.998; p<0.001), WBC (t: 2.166; p=0.031) and DM existence (t: 2.749; p=0.006).

Discussion

The purpose of the study was to draw attention to the overlooked high rates of HBcAb positivity in hemodialysis patients consisting of immune-compromised individuals. In our cohort, we found no HBV-DNA and therefore OBI cases in patients with positive HBcAb. On the other hand, although it was not clearly known if patients were exposed to HBV before or after the initiation of dialysis, we found high rates of positive HBcAb. Despite the low number of patients, 59 of 241 (24%) patients were with positive HBcAb, 2 of them (0.8%) were with isolated positive HBcAb.

In our study, patients with positive HBcAb were older compared to patients with negative HBcAb. This may be due to the higher chance of being exposed to HBV. There is a strong association of DM with age (11). This may be the reason of the statistically significant difference between groups in terms of DM in our cohort.

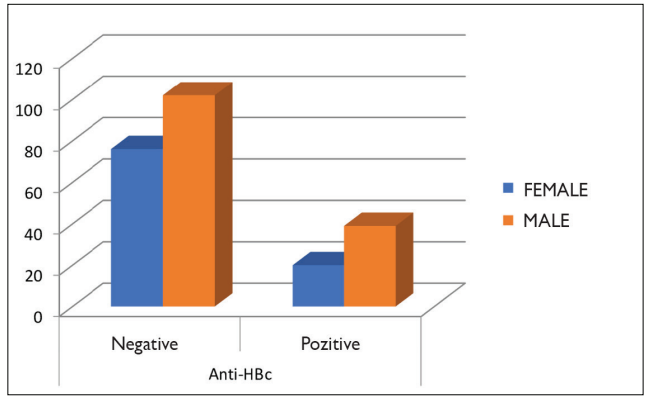

Figure 1. Distribution of patients in group 1 and group 2 in terms of gender
Anti-HBc: Anti-hepatitis B core

Table 1. Demographical and laboratory results of HBcAb positive and HBcAb negative patients

	HBcAb positive (n=59)	HBcAb negative (n=178)	p
Age (years), mean ± SD	64±11	60±15	**0.018***
Gender F/M	34/66	43/57	0.230
AST (U/L) [Median (IQR)]	10 (8)	13 (8)	**0.020****
ALT (U/L) [Median (IQR)]	8 (7)	10 (7)	**0.046****
HbA1c (%), mean ± SD	8.5±1.3	8±1.2	0.151
Kt/V (min: 1.2), mean ± SD	1.5±0.3	1.6±0.4	0.104
URR (%) (min 65%), mean ± SD	71±7	72±8	0.490
HBsAb Titer (m IU/mL) [Median (IQR)]	196.6 (469.1)	136.2 (425.6)	0.111
Transfusion history n, (%)	81%	85%	0.528
DM n, (%)	32%	19%	**0.036*****
Albumin (g/dL), mean ± SD	3.8±0.5	4.1±2.9	0.395
Hemoglobin (g/dL), mean ± SD	11±2	11±1.8	0.690
Hematocrit (%), mean ± SD	33±6	33±5	0.984
Platelet (x103/μL), mean ± SD	227±71	222±72	0.644
WBC (x103/μL), mean ± SD	7.7±2.5	7.1±2.1	**0.044***

F: Female, M: Male, AST: Aspartate transaminase, ALT: Alanine aminotransferase, URR: Urea reduction ratio, DM: Diabetes mellitus, WBC: White blood cell count, IQR: interquartile range, HBcAb: Hepatitis B core antibody, SD: Standard deviation, *: Student's t-test was used and significantly higher result was found in HBcAb positive group, **: Mann-Whitney U test was used and significantly higher result was found in HBcAb negative group, ***: The chi-square test was used and significantly higher result was found in HBcAb positive group

The immunosuppressive nature of chronic kidney disease (CKD) is due to the combined effects of many factors including chronic inflammation, uremia and dysfunction of both adaptive and innate immune system (12).

CKD results in a state of immunosuppression that is likely multifactorial due to a combination innate and adaptive immune system dysfunction, chronic inflammation, endothelial cell dysfunction and uremia (12). Since hemodialysis patients are immune suppressed patients, they are in the high-risk group for OBI reactivation. Although we detected no positive HBV-DNA, these high rates of positive HBcAb carry a high risk of HBV reactivation and possible adverse clinical outcomes.

Conventional serologic testing used in most dialysis centers is not able to identify the OBI (13). HBcAb was shown to be a useful marker for the detection of OBI in the literature (14). In a study, 996 healthy blood donors were evaluated and 2.4% revealed isolated positive HBcAb. Two of 23 patients (8.6%) were with positive HBV-DNA (15). Tarif et al. (16) evaluated the prevalence of isolated positive HBcAb status in non-vaccinated CKD patients in terms of previous exposure and found 51% among HBsAg negative CKD patients. In our study, we found 2 (0.8%) patients with isolated positive HBcAb, who were non-vaccinated. The reason why the rates of isolated positive HBcAb in our cohort were found relatively low might be due to the tight vaccination program of hemodialysis patients.

Studies in the literature about the OBI prevalence among hemodialysis patient era revealed low level of OBI. In a study, Aghakhani et al. (17) detected OBI in 50% of patients with positive anti-HBcAb. On the other hand, in agreement with our study, neither Fabrizi et al. (18) nor Jardim et al. (19) found positive HBV-DNA in their hemodialysis patients with positive HBcAb. Ramezani et al. (20) found 1% of patients on hemodialysis had OBI with positive HBV-DNA. The clinical importance of OBI depends on its' possible consequences associated with immune status. In the literature, although HBsAb was positive, both HBV transmission from OBI cases and HBV reactivation under immunosuppressive therapy in patients with OBI were shown in the studies (21). This reflects the importance of HBcAb screening even in patients with positive HBsAb. Also, dialysis patients may receive a kidney transplant at a later time in their course. Having an HBV infection may affect several aspects on their kidney transplant care in which immune suppressive medications are used to avoid rejection. Therefore, positive HBcAb, either isolated or with positive HBsAb, should be taken into account in immune-compromised patients such as dialysis patients and the possibility of OBI should be excluded be checking HBV-DNA.

In fact, patients with positive isolated HBcAb those admitted to the hospital with immediate need of dialysis, should be dialyzed on HBV positive machines in order to avoid exposing HBsAg negative patients to potential infection. Hypo-transaminase is a well-recognized feature in dialysis patients with or without liver disease. The normal range of transaminases should be adjusted downwards; otherwise, the incidence or severity of clinical liver disease might be underestimated. In this regard, levels of 24 and 17 IU/L have been recommended as the upper limits of normal AST and ALT levels, respectively, in dialysis patients (10). In our study, mean AST and ALT levels in HBcAb positive and HBcAb negative patients were 10 (8) U/L vs 13 (8) U/L and 8 (7) U/L vs 10 (7) U/L, respectively.

The OBI prevalence was found to be increased in patients with positive HCV probably due to the inhibition of HBV replication via interference of HCV in the hepatocyte (22,23).

On the contrary, in the literature, there are several studies those found no association between HCV and OBI (24-26). In our study, there were 3 patients with HCV. None of them were with either positive HBcAb or HBV DNA. This might be due to the insufficient number of patients with HCV in our cohort. Elevation of markers associated with liver damage may not be seen in dialysis patients due to suppression of inflammatory reactions due to chronic uremia (27). For this reason, to rule out OBI, HBV-DNA testing is crucial in dialysis patients (28). This can be considered as another justification for the necessity of administering HBV-DNA in the routine evaluation of hemodialysis patients with positive HBcAb.

In the literature, in vast majority of OBI cases serum viral load was reported about 20 IU/mL or undetectable (29). In our study, we found no viral load in patients with positive HBcAb. This might be due to fluctuation of viral load or relatively small number of patients.

Using erythropoiesis-stimulating agents in dialysis patients resulted in diminished need for transfusion. In addition, tight vaccination programs and screening blood products for viral markers contributed to decreasing of HBV infection in dialysis. In our study, we evaluated the transfusion rates and found no a significant difference between groups. Between groups, there was significant difference in terms of HBsAb titers. This may be due to the contribution of natural immunity after exposure to HBV to vaccination-associated immunity in patients with positive HBcAb. Also, we evaluated the mean time after the last vaccination dose and its' correlation with antibody titers and found no statistically significant difference between patients with positive HBsAb. The mean antibody levels were above the protective levels, which is accepted to be above 100 IU/L, at both groups. This may be related to

tight vaccination program and close follow-up procedures in our cohort.

Study Limitations

Number of patients was relatively small in our cohort. Also, we could not rule out seronegative OBI because not of not checking HBV-DNA in patients with HBcAb and HBsAb are both negative.

Conclusion

Due to the risk of viral reactivation, the importance of HBcAb should not be underestimated particularly in patients with immune suppression such as dialysis patients. HBsAg and HBcAb must be checked together. In addition, HBV-DNA testing should be performed in patients with positive HBcAb.

Authorship Contributions

Concept: I.B., S.T., Design: I.B., Data Collection or Processing: I.B., Analysis or Interpretation: I.B., S.T., Literature Search: I.B., S.T., Writing: I.B.

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Original Article

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Comparison of Upper Elbow Cast and Splint in Type II Supracondylar Humerus Fractures in Pediatric Patients

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Abstract

Aim: Most of the childhood elbow area fractures constitute supracondylar humerus fractures. The treatment approach in Gartland type II fractures is controversial. The purpose of our study was to compare the effectiveness of cast and splint in conservative treatment of type II supracondylar humerus fractures.

Methods: Sixty-nine pediatric patients admitted to our clinic due to gartland type II supracondylar humerus fractures between 2015 and 2020 were retrospectively evaluated. Closed reduction upper-elbow cast was applied to 26 patients, and closed reduction upper-elbow splint treatment was applied to 43 patients. Radiological results of the patients were compared.

Results: The mean age of the patients participating in the study was 4.86±2.61. Forty-two of 69 patients were male and 27 were female. Neurovascular deficit and compartment syndrome were not observed in any of the patients. When compared radiologically, no significant difference was found between the two groups.

Conclusion: Type II supracondylar humerus fractures, where conservative treatment is planned, the upper elbow casting or splint selected for immobilization shows similar effectiveness in protecting reduction.

Keywords: Humerus fracture, conservative treatment, classification

Introduction

Supracondylar humerus fractures constitute 30% of childhood fractures between the ages of two and eight years, and most of the fractures in the elbow area in childhood (1,2). The Gartland classification is used in the classification of these fractures (3). This classification classifies non-displaced fractures as type I, fractures with varying degrees of displacement, but type II in which the posterior cortex is intact, displaced fractures in which the entire cortical connection is broken all around as type III.

In Gartland type I fractures, fixation in the position it is, and in Gartland type III fractures, open or closed reduction and pinning are the generally accepted treatment approaches (4-6). The treatment approach in type II fractures is controversial. Some authors recommend the closed reduction and pinning in all type II fractures with its success in achieving and maintaining reduction and low complication rates (7,8). Some authors, on the other hand, argue that successful results are obtained in many patients with closed reduction and immobilization, therefore, avoiding the morbidity caused by surgical approach in this patient group would be a more appropriate approach (9,10).

In our clinic, the Blount technique (closed reduction and immobilization) is used in the approach to type II supracondylar humerus fractures (11). For immobilization after reduction, an over-elbow circular cast or an over-elbow splint is used in patient groups. The aim of this retrospective, radiological outcome study is to compare the effectiveness of the above-elbow plaster and splint in protecting the reduction achieved.

Methods

Study Design

Our study was prepared retrospectively in accordance with the ethical standards of the University of Health Sciences

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Turkey, Haseki Training and Research Hospital Clinical Research Ethics Committee and 1975 Helsinki Declaration revised in 2013, and the ethics committee approval was obtained (decision no: 2020-26, date: 26/02/2020). Since it is a retrospective study, only patient consent is available. Pediatric patients admitted to the emergency department between 2015 and 2020 and treated for supracondylar humerus fractures were scanned using hospital digital records and patient files. Patients with Gartland type I and type III fractures and other accompanying traumas were excluded from the study. Sixty-nine patients with non-surgically treated Gartland type II fractures, who had control films before, after reduction, and at the third week, followed up with an over-elbow splint or cast at 90° after reduction, were included in the study (Figure 1). Demographic characteristics of the patients were noted. During the follow-up, the development of neurovascular complications and compartment syndrome was checked using hospital digital records and patient files. Depending on the preference of the treating surgeon, the patients were followed up with either an over-elbow circular cast or an over-elbow splint after reduction.

Radiological Assessment

Two researcher physicians accessed the pre-reduction, post-reduction and third-week graphs of the patients through the image archiving and communication system of our hospital. Baumann angle and anterior humeral line were used in radiological follow-up (Figure 2). The normal value was determined as 72±4 as the Baumann angle. 10° rotation in the humerus causes 6° change in the Baumann angle. For this reason, a change greater than 6° in post-reduction and final graphs was considered as a significant loss of position. Changes between 6° -12° were noted as mild, changes greater than 12° were noted as severe reduction loss. On the lateral graph, the capitellum was divided into three equal parts and where the anterior humeral line intersected the capitellum was noted. Middle 1/3 slice was considered normal. A one-slice change was considered a mild, two-slice change during follow-up was considered a serious loss of position.

Statistical Analysis

SPSS version 21.0 program was used for statistical analysis. While evaluating the study data, besides descriptive statistical methods (average, standard deviation, median, frequency, ratio, minimum, maximum), the Repeated Measures test (Variance Analysis in Repeated Measures) in the evaluation of the follow-up of the variables showing normal distribution in the comparison of quantitative data and Bonferroni test in the evaluation of paired comparisons Friedman test and Wilcoxon-Signed Ranks test were used to evaluate the follow-up of variables that did not show normal distribution. Significance was evaluated at the $p<0.05$ level.

Results

Sixty-nine patients were included in the study. After the reduction, 26 of the patients were followed with a cast and 43 with a splint. The mean age of the patients participating in the study was 4.86±2.61 (1-12). 42 of 69 patients were male and 27 were female. Neurovascular deficit and compartment syndrome were not seen in any of the patients. The Baumann angle of 69 patients was 69.91±629 before reduction, 69.85±5.46 after reduction and 70.05±5.42 at the 3rd week follow-up. Again, when all patients were examined, before reduction, the anterior humeral line was anterior to the capitellum in 31 patients, the anterior 1/3 of the capitellum in 33 patients, and the middle 1/3 in 5 patients. After reduction, it was anterior to the capitellum in 14 patients, anterior 1/3 in 41 patients, and middle 1/3 in 14 patients. In the last follow-up, it was in front of the capitellum in 11 patients, in the anterior 1/3 in 43 patients, and in the middle 1/3 in 15 patients. Baumann angles belonging to the cast and splint group and the change in the intersection of the anterior humeral line with the capitellum are summarized in Table 1.

When the success in preserving the reduction obtained in the coronal plane in the splint and cast group

Table 1. Changes in the radiographs. Baumann angle and anterior humeral line-capitellum intersection in the cast and splint group before after reduction and at the third-week follow-up

	Before reduction				After reduction				Third week follow-up			
	Baumann angel	Anterior humeral line			Baumann angel	Anterior humeral line			Baumann angel	Anterior humeral line		
		Middle 1/3	Anterior 1/3	Anterior to the capitellum		Middle 1/3	Anterior 1/3	Anterior to the capitellum		Middle 1/3	Anterior 1/3	Anterior to the capitellum
Cast	69.11±7.41	2	11	13	68.14±5.85	0	13	13	67.58±4.40	0	17	9
Splint	70.39±5.55	3	22	18	70.88±5.00	14	28	1	71.55±5.49	15	26	2
*No difference between groups in repeated measurements in Bauman angles (p=0.287)												

was compared with the Baumann angle, no significant difference was found between the two groups (p=0.743) (Table 2). When the radiological results of all patients were evaluated, it was found that reduction could be preserved in 58 patients (84%), and serious reduction loss was found in only three patients (4%). The quality and loss of reduction in the sagittal plane were followed by the anterior humeral line. Between the cast and splint groups, there was no significant difference between the groups in preserving the reduction obtained in the sagittal plane (p=0.161) (Table 2). While no significant change was observed in the lateral graphy in 59 (86%) of 69 patients, minimal reduction loss was observed in 10 patients (14%).

Discussion

There is no consensus in the literature on the approach to Gartland type II fractures. Miranda et al. (12) reported in their study that they obtained radiological and functional results similar to those who were treated surgically in patients followed up with conservative treatment. Hadlow et al. (9) reported that surgical treatment of all type II fractures caused unnecessary surgical intervention in 77% of patients. Ojeaga et al. (13) described the factors affecting the success of conservative treatment in type II supracondylar humerus fractures and reported that conservative treatment had similar results to surgical treatment. Parikh et al. (5) experienced reduction loss in

Table 2. Comparison of the anterior humeral line and Baumann angle measurements with the measurements of the third week after reduction

		Cast	Splint	p
		n (%)	n (%)	
Anterior humeral line	Reduction preserved	20 (76.9%)	21 (80.8%)	0.161
	Minimal reduction loss	6 (23.1%)	4 (15.4%)	
	Severe reduction loss	0 (0.00%)	1 (3.8%)	
Baumann angle	Reduction preserved	39 (90.7%)	37 (86%)	0.743
	Minimal reduction loss	4 (9.3%)	4 (9.3%)	
	Severe reduction loss	0 (0.00%)	2 (4.7%)	

28 of the patients with type-two supracondylar humerus fractures they treated conservatively, and late surgical approach was required in 20% of the patients. In the radiological studies of Camus et al. (4), approximately half of the conservatively treated patients had rotational plane deformity in the coranal plane and sagittal plane deformity in 80%, and they recommended a surgical approach in treatment. Morrison et al. (14) stated that the complication rate of surgical treatment is quite low contrary to popular belief and they advocated the surgical approach. Skaggs et al. (15) surgically treated all type II supracondylar humerus fractures in their study and did not observe any position loss in any patient, pin tract infection developed in 2.1% of the patients and secondary surgical intervention was required in 0.5% of the patients. They advocated a surgical approach in the treatment of these fractures due to low complication rates and better radiological results (15).

In the final follow-up of our study, the alignment of 58 patients (84.05%) in the coronal plane was found to be within normal limits. The success rate was lower in the sagittal plane. In only 15 of the patients (21.7%), the anterior humeral line passed through the middle 1/3 of the capitellum. Although it is not sufficient by itself to demonstrate the reduction quality of the anterior humeral line, the success of conservative treatment in preventing extension deformity in the sagittal plane has been found to be lower than in the literature (4,16). Although none of the patients had compartment syndrome or neurovascular injury seen as the positive side of conservative surgery, achieving and maintaining anatomical reduction was observed to be lower than surgical treatment.

When conservative treatment is chosen in type II supracondylar humerus fractures, the preferred method for immobilization is usually an above-elbow cast (4,5,8). We compared the radiological results of these two patients groups to find out whether the above-elbow splint to be selected in the same patient group showed similar success in treatment in order to avoid difficulties in applying and removing the cast and to avoid possible complications such as compartment syndrome that may develop due to the cast. In both methods, the reduction obtained in more than 75% of the patients in the sagittal plane and more than 80% in the coronal plan could be preserved. While there was no serious loss of position in any patient in the sagittal plane, serious position loss was observed in one patient in the cast group in the coronal plane and in two patients in the splint group. There was no significant difference between groups in maintaining the reduction. This study shows that the above-elbow splint and cast used for immobilization after reduction in Gartland type II supracondylar humerus fractures are similarly effective in preserving reduction. Roberts et al. (17) compared cast and flexion-taping and immobilization in type II supracondylar humerus fractures and reported similar success rates in achieving and maintaining reduction in both patient groups.

We did not find any study comparing immobilization with splint and cast in the same patient group in the literature. In this respect, we think that the results of our study will contribute to the literature.

Limitations of the Study

The most important limitation of our study is that it is a retrospective study. In addition, the fact that the patient groups are not determined randomly and the treatment is determined according to the surgeon's preference is another important limitation. Our limited number of patient groups makes it difficult to compare the rare complications according to the groups. A higher number of patient series are required to tell whether there is a difference between the groups in this regard. In addition, our study only evaluates radiological results. In order to compare both treatments, prospective randomized studies planned with a large number of patient series are needed in which functional results are examined.

Conclusion

In Gartland type II supracondylar humerus fractures, the success of conservative treatment to achieve anatomic reduction, especially in the sagittal plane, is low. In this group of patients for whom conservative treatment is planned, we believe that the above-elbow cast or splint selected for immobilization has a similar feature in protecting reduction.

Authorship Contributions

Concept: E.B., M.Y., Design: E.B., M.Y., M.A., Data Collection or Processing: M.A., M.Er., M.E., C.Y., Analysis or Interpretation: M.A., M.Er., M.E., C.Y., Literature Search: M.Er., M.E., C.Y., Writing: E.B.

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Case Report

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Drug-Associated Thrombocytopenia as a Rare and Devastating Side Effect of Octreotide in a Cirrhotic Patients: A Case Report and Current Literature Review

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Abstract

Variceal bleeding is one of the most serious outcomes encountered in portal hypertension. It represents one of the leading causes of death in cirrhotic patients. Octreotide infusion is the mainstay of treatment in variceal bleeding. It shows its effects by lowering portal venous pressure. Here, we present a patient with variceal bleeding who experienced sudden thrombocytopenia after octreotide infusion. Cessation of the octreotide therapy has resulted in a quick recovery of the platelet counts. Naranjo adverse drug reaction probability scale has revealed a probable relationship with 6 points. The case is reported in discussion with the existing 4 cases in the literature.

Keywords: Octreotide, thrombocytopenia, esophageal varices, liver cirrhosis

Introduction

Variceal bleeding is one of the most detrimental complications of portal hypertension. Variceal bleeding is associated with a 30-day mortality rate reaching 20 percent (1). Treatment consists of supportive management (i.e. saline, blood products), proton pump inhibitors and somatostatin analogs, namely octreotide. Somatostatin and octreotide help achieve hemostasis and prevent re-bleeding but neither have clearly shown benefit on mortality (2,3). Somatostatin and octreotide are generally well tolerated with minimal side effects. Although they have several common side effects, namely gallbladder stone and hyperglycemia, thrombocytopenia is not frequently encountered with only a few case reports in the literature.

Case Reports

A 76-year-old male patient with prior medical history of cirrhosis due to hepatitis C virus infection, familial Mediterranean fever, chronic obstructive pulmonary disease, hypertension and prostate adenocarcinoma was admitted to our hospital with recent onset melena. He had child-pugh class B cirrhosis with prior episode of variceal bleeding. Initial vital signs on admission were blood pressure of 100/60 mmHg, heart rate of 125 bpm, respiratory rate of 20 breaths/minute and oxygen saturation of 97 percent on ambient air. His physical examination was non-revealing apart from mild ascites. Laboratory findings on admission were hemoglobin level of 4.5 g/dL, platelet level of $156x10^3$/μL, and INR of 1.5. He received 1.5 liter of saline, 3 units of packed red blood cells, IV pantoprazole 80 mg bolus followed by 8 mg per hour and IV octreotide 50 μg bolus IV injection followed by continuous infusion at a rate of 50 μg per hour. Upper gastrointestinal endoscopy revealed non-bleeding esophageal varices and they were treated with band ligation with no treatment-related complication. Shortly after the initiation of octreotide treatment, platelet counts showed a fall trend with level of $108x10^3$/μL on the first day, $84x10^3$/μL on the second day and finally $63x10^3$/μL on the third day (Figure 1). The patient was consulted to the hematology department with laboratory tests, including a peripheral blood smear and coagulation panel which did not reveal any abnormalities. There

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were no possible medicines likely to contribute to new onset thrombocytopenia. Octreotide was discontinued on the third day with possible diagnosis of drug-induced thrombocytopenia. Following cessation of the drug, platelet counts dramatically improved, reaching 84x10^3/μL on the first day of the withdrawal, 109x10^3/μL on the second day and finally 146x10^3/μL on the third day. Written consent was obtained prior to discharge in order to write this study.

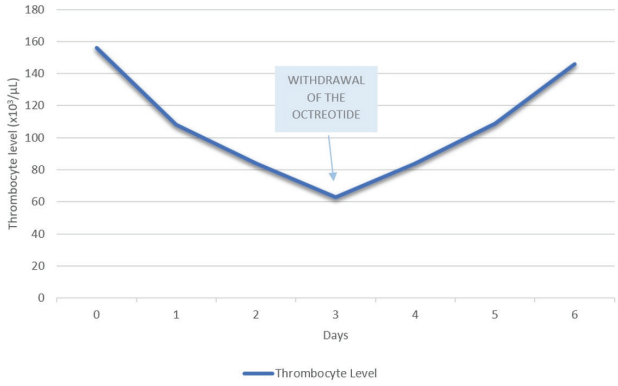

Figure 1. The course of platelet counts over time

Discussion

Thrombocytopenia related to octreotide infusion is an extremely rare and presumably overlooked adverse effect. Several case reports have been published with different characteristics were shown in Table 1 (4-7). While these studies show differences in time to nadir and recovery time of thrombocytes, they all report abrupt drop of thrombocytes shortly after introduction of octreotide and prompt initiation of recovery with the removal of octreotide, both consistent with our case. The mechanism of thrombocytopenia due to octreotide is mainly immunologic (8). Drug-induced thrombocytopenia refers to accelerated platelet wasting by antibodies that bind to glycoproteins on platelet cell membranes (9). Taking into consideration the fact that cirrhotic patients usually tend to become thrombocytopenic, any further insult leading to bleeding diathesis may lead to deleterious consequences. Naranjo adverse drug reaction probability score is a tool to assess whether a reaction is linked to the exposed drug (10). Scores are reported as ≤0 (i.e. doubtful), 1-4 (i.e. possible), 5-8 (i.e. probable) and ≥9 (i.e. definite). We calculated the score as 6, which reveals a probable link between octreotide and thrombocytopenia Appendix 1. Physicians must keep in mind that fall of thrombocyte levels shortly after octreotide infusion may be due to drug-induced thrombocytopenia and may require prompt withdrawal of drug.

Table 1. Case reports accessed via PubMed database. Note that platelet levels decrease more than 50% in 3 cases and 49% in 1 case

Author	Year	Number Of patients	Indication for octreotide therapy	Platelet level on admission (per mm^3)	Octreotide therapy duration (days)	Nadir platelet level (per mm^3)	Days to nadir	Days to platelet Recovery (after cessation of octreotide)
Hanna WT. et al (4)	1990	1	Enterocutaneous fistula	204.000	10	56.000	10	9
Demirkan K. et al (5)	2000	1	HCV induced cirrhosis	122.000	6	62.000	2	5
Chisholm S. et al (6)	2009	1	Alcohol-induced cirrhosis	144.000	3	28.000	5	N/A
Rashidi A. et al (7)	2011	1	Alcohol-induced cirrhosis	155.000	3	50.000	3	2

N/A: Not available, HCV: Hepatitis C virus

Authorship Contributions

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

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Appendix 1. Naranjo adverse drug reaction probability scale result of the patient					
	Question	**Yes**	**No**	**Do not know**	**Score**
1.	Are there previous conclusive reports on this reaction?	+1	0	0	+1
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
3.	Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
4.	Did the adverse event reappear when the drug was re administered?	+2	-1	0	0
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	+2
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	0
7.	Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8.	Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	0
TOTAL SCORE					+6

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