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KASTAMONU MEDICAL JOURNAL

Review

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Hereditary dystrophies of the posterior segment of the retina

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ABSTRACT

Hereditary dystrophies of the posterior segment of the retina are the common name for a group of syndromic diseases in which the retina is affected. There used to be a few know-hows and wide clinical findings in these diseases. Current genetic developments herald good promising results. In this text, you will find the ciliopathies group (Bardet- Biedl, Usher, McKusick Kaufman, Alström, Joubert, Senior Loken syndromes), Bassen Kornzweig (Abetalipoproteinemia), albinism, neuronal ceroid lipofuscinosis, mucopolysaccharidoses, peroxisomal disorders, cystinosis, and mitochondrial diseases.

Keywords: Dystrophy, hereditary dystrophies, posterior segment, retina

INTRODUCTION

Hereditary dystrophies of the posterior segment are the common name for a group of syndromic diseases in which the retina is affected. Developments in the field of genetics have increased the knowledge about these diseases, which has facilitated the diagnosis of these diseases, but the necessity to classify the diseases has emerged. The dominance of molecular methods in the diagnosis of these diseases facilitated the understanding of the pathophysiology of the diseases. In addition, it is easier to predict the prognosis of the disease by scanning responsible candidate genes. In the classification of diseases, a more objective classification can be made by molecular methods. In addition to all these benefits, it has become easier to provide information to patients in clinical practice (1).

Traditionally, these diseases have been classified according to the anatomical level to which the retina is affected: retina, macula, choroid, retinal pigment epithelium (RPE), etc. However, many dystrophies show the same characteristics and take place in a wide variety of quadrants, making this classification difficult and inadequate for classification. Molecular studies conducted with family history, a detailed examination, and electrophysiological studies provide a diagnosis of these diseases (1).

Hereditary diseases of the eye display substantially bilateral and symmetrical involvement. When unilateral ocular findings are detected, intrauterine/antenatal infection, inflammatory diseases, and birth trauma should be considered (2).

The characteristics of the genetic defects (where the gene is located, its expression, localization, and mutation) that form the basis of retinal dystrophies cause the diseases to differ phenotypically. For example, in the gene mutation of RDS/peripherin, retinitis pigmentosa, pattern dystrophy, and rod-cone dystrophy occur, while changes such as juvenile or adult-onset type occur due to the mutation in the ABCA-4 (Stargardt) gene (2).

In this review, fundus dystrophies secondary to hereditary metabolic diseases are discussed. In addition, current information on these diseases is presented. Some of these diseases are Bassen-Korzwieg, Bardet Biedl Crystalline Retinopathy, Alport syndrome, Keans Sayre syndrome, Usher Syndrome, Friedreich Ataxia, Homocystinuria, Mannosidosis, Mucopolysaccharidosis 1-2-3, Neuronal ceroid, Refsum Disease, Zellweger. (1-3).

Diagnostic and Prognostic Tests

Electroretinogram (ERG) and kinetic visual field (GA) tests were found useful in the diagnosis of hereditary retinal and choroidal dystrophies. ERG test is performed in two stages, scotopically and photopically, and a total of five measurements are taken. Three measurements (rod, combined rod-cone, and flicker) are made scotopically and two measurements are made photopically (con and con oscillation). In addition, genetic sequencing and gene knowledge and faulty and mutated areas in DNA can be detected by PCR and other diagnostic methods (4).

A) Bardet- Biedl Complex

Bardet - Biedl complex is an autosomal recessively inherited ciliopathy that affects rod and con cells with a prevalence of 1 / 125,000 (5)

The defect in the transport of phototransduction proteins from the inner segment to the outer segment in photoreceptor cells causes cell death, and this is the underlying cause of pigmentary retinopathy in Bardet Biedl Syndrome (6)

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Clinical findings of this disease are; pigmentary retinopathy, obesity, polydactyly, hypogonadism, and mental retardation. Pigmented retinopathy is observed in 90% of the patients. It begins mostly in childhood. In the newborn period, the fundus has a natural appearance. The first changes are optic disc pallor and nonspecific changes in the macular pigment epithelium (7)

The Bardet - Biedl complex has a wide phenotypic distribution. Obesity and polydactyly are the most diagnostic finding (8)

At least 19 gene mutations related to this disease, previously classified in the autosomal recessive family, have been identified. These genes are named BBS1-19. The treatment is symptomatic. They receive the same treatment as a society for obesity, hypercholesterolemia, diabetes, and hypertension (7)

Genetically Related Disorders with Bardet Biedl

There are many phenotypic and molecular similarities of Bardet Biedl and other diseases related to cilioptic pathologies. Genetic anomaly variations that cause Bardet Biedl syndrome to lead to other ciliopathologies. McKusick- Kaufman, Alstrom, Meckel-Gruber, Joubert, and Senior Loken syndromes are included in this group.

a) **McKusick - Kaufman Syndrome:** Hydrometrocolpos is characterized by congenital heart disease and postaxial polydactyly. Variants in the BBS6 gene are associated with this clinic (4-6).

b) **Alström Syndrome:** Rod-Cone dystrophy, truncal obesity, progressive sensorineural hearing loss, dilated cardiomyopathy, insulin resistance, and developmental retardation are seen. Kidney and liver failure are common in the late stages of life. Polydactyly is not observed in this syndrome (4-6).

c) **Joubert Syndrome:** It is a rare clinical variant. Different mutations in 18 genes that trigger this syndrome have been shown. Infantile irregular breathing, developmental retardation, intellectual developmental retardation, ataxia, cerebellar and brainstem developmental disorders, hypotonia, oculomotor apraxia, given hypoplasia or agenesis can be observed. Ocular coloboma and occipital encephalopathy are the most severe clinical conditions. NPHP1, AHI1, CEP290 (NPHP6), TMEM67 (MKS3), RPGRIP1L, CC2D2A, ARL13B, INPP5E, OFD1, TMEM216, KIF7, TCTN1, TCTN2, TMEM237, CEP4, TMEM138, CPLANE1 are the most common mutation genes (4-6).

d) **Senior Loken Syndrome:** It is another rare syndrome. It has features that overlap with Joubert and Bardet-Biedl syndrome. Six gene mutations were identified. The main clinical features are retinitis pigmentosa and renal diseases. Cerebellar hypoplasia, ataxia, developmental retardation, and intellectual disability are common features. CEP290, NPHP1, NPHP3, NPHP4, SDCCAG8 are the most common mutation genes (7,8).

B) Bassen Kornzweig Syndrome

Abetalipoproteinemia is a rare autosomal recessive disease. Beginning from infancy, chylomicron, low-density lipoprotein, and ADEK vitamin deficiencies are detected. A mutation is observed in the gene encoding the large lower part of the microsomal triglyceride transfer protein (MTTP). This biallelic protein is essential for the function of the ApoB protein, which is found in chylomicron and very-low-density lipoprotein structure and provides its transport. At the present, at least 33 mutations encoding this gene have been identified. The mutation is detected by gene-targeted screening or sequence analysis (9).

In the early period, steatore, developmental retardation, and spinocerebellar ataxia are seen. Also, pigmented retinopathy (PR) ophthalmoplegia and nystagmus are seen. Acanthocytes are observed in peripheral smear (10).

C) Usher Syndrome

Retinitis pigmentosa is seen with congenital, partial, or significant hearing loss. The disease develops due to the mutation of the genes that are responsible for the synthesis of cadherin, usherin, whirlin, clarin-1, harmonin proteins. At present, 14 different gene mutations causing this syndrome have been identified. Usher is a ciliopathy like Bardet Biedl and associated syndromes (5)

There are 3 subtypes of the disease. There are signs of type 1 congenital sensorineural complete deafness, vestibular dysfunction, and typical retinitis pigmentosa. Type 2 has mild to severe hearing loss and typical signs of retinitis pigmentosa. In type 3, there is progressive hearing loss and typical retinitis pigmentosa (11).

With MYO7A (USH1B), CDH23 (USH1D), PCDH15 (USH1F), USH1C (USH1C) and USH1G (USH1G) USH type 1. The 3 genes named USH2A (USH2A), GPR98 (USH2C), and DFNB31 (USH2D) are related to USH2. USH3 is a clinical syndrome that is rarely seen in the general population and the USH3A gene is responsible (12,13)

In addition to Usher syndrome, many genetic disorders have pigmented retinopathy and hearing loss. The most common of these are: Alport, Alstrom, Cockayne, Hurler, and Refsum diseases (12)

D) Albinism

Albinism is used to describe a group of diseases with or without melanin pigment synthesis. Decreased melanin synthesis may affect the eye, skin, and hair follicles. If the skin and hair follicles are pigmented normally and isolated eye involvement is seen, it's called ocular albinism. In all types of albinism, nerve fibers from the temporal of the retina create cross paths, as they will project to the lateral corpus geniculate (14).

Albinism eye involvement generally takes two forms:

1) Congenital subnormal visual acuity and albinism

2) Normal or minimally reduced visual acuity without nystagmus

Photophobia, transillumination defect, and fundus hypopigmentation are common in both types. These two types can also be divided according to the development of fovea. In the first type, the fovea is hypoplasic, no foveal cupping and reflux is observed. In addition, the luteal pigment is not found in the fovea (15).

At least 9 separate gene mutations causing ocular and oculocutaneous albinism have been identified. Ocular albinism is generally recessively linked to X. There are types of oculocutaneous albinism that are tyrosinase negative and tyrosinase positive. While hypopigmentation is detected in both types in childhood, pigment can be stored in skin, hair, and iris with age in those who are tyrosinase positive. Visual acuity is better in those with more pigment accumulation in RPE in the posterior segment. These patients also have a decrease in nystagmus. Albinism is a component of the hematological

disorders, Higashi and Hermansy Pudlak syndrome. When these two types are suspected, hematological evaluation must be performed (16).

E) Neuronal Ceroid Lipofuccinosis (Batten Disease)

Batten Disease is the most common neurodegenerative lysosomal storage disease of childhood, in which lipopigments accumulate in the lysosomes of neurons and other cells. Ceroid and lipoprotein accumulation causes loss of cell function and as a result, apoptosis occurs. In early-onset cases, pigmented retinopathy, vision loss, progressive dementia, and seizures are detected. Along with clinical findings, diagnosis is made by examining tissues taken by peripheral smear and conjunctival biopsy under electron microscopy.

It is divided into subtypes according to the age of onset.

a) Haltia Santavuori in infancy

b) Childhood Jansky-Bielschowsky

c) Preschool period Lake - Cavenagh

d) School term Spielmeyer - Vogt-Batten (17)

There is no ocular finding in preschool and school patients. In the other two subtypes, optic atrophy, spotting on the retina, and retinal pigment epithelial changes in the macula are observed (18).

F) Peroxisomal Diseases and Refsum Disease

The basis of many systemic pathologies associated with eye findings in childhood may be due to the defect of peroxisomes of cellular organelles. Peroxisomal diseases are diseases that progress with the accumulation of long-chain fatty acids due to deficiencies in peroxisomes or peroxisomal enzyme functions. They are examined in three subgroups;

1. Those due to errors in Peroxisome biogenesis (Zellweger disease, newborn adrenoleukodystrophy, infantile Refsum)
2. Those connected with multiple enzyme defects (Rhizomelic chondrodysplasia punctate)
3. Those connected to a single enzyme defect (X-linked adrenoleukodystrophy, Primary hyperoxaluria type1)

Zellweger's disease is the prototype and most severe of the peroxisomal diseases. In Zellweger Syndrome, psychomotor retardation, seizures, retinal degeneration, hypotonia, renal and hepatic cysts are observed and usually end up in death in the first year. Eye findings are corneal opacity, cataracts, glaucoma, pigmentary retinopathy, and optic atrophy. Neonatal Adrenoleukodystrophy and infantile Refsum are seen with symptoms similar to Zellweger's disease, and different genetic disorders are effective in these diseases. In addition, clinical findings are milder.

Serum phytanic acid levels are increased in Refsum disease. Pigmentary retinopathy, polyneuropathy, cerebellar ataxia, anosmia, hearing loss, and cardiomyopathy are seen. Diagnosis is made by determining the plasma phytonic acid level or the low level of phytanic acid oxidase activity in fibroblast culture. Clinical stabilization is achieved by removing phytanic acid precursors from the diet.

There are congenital skeletal anomalies in rhizomelia chondrodysplasia puncta and death is common after 1 year of age. The most common ocular finding is cataracts.

In X-linked adrenoleukodystrophy, a decrease in behavioral and cognitive functions in the late period of the first decade of life is accompanied by poor vision. Low vision is seen due to the demyelination of all visual pathways (19).

G) Mucopolysaccharidosis

In mucopolysaccharidoses arising in consequence of defects in genes encoding lysosomal mashes, glycosaminoglycans are stored in lysosomes together with lipoproteins due to the destruction abnormality.

Retinal changes are observed only in the types that go with heparan sulfate accumulation. Among these, Hurler and Scheie Syndromes are characterized by rough face, mental retardation, corneal turbidity, and retinal degeneration.

Pigmented retinopathy is seen in Hunter Syndrome, but turbidity is not observed in the cornea.

Tay - Sachs is the most common ganglioside storage disease, perifovea area is observed pale due to the gangliosides accumulated in the ganglion cells around the fovea. Since the foveal reflux is preserved, a Japanese flag or cherry red sign is encountered.

While brain involvement is not observed in the adult types of Gaucher Disease, reticuloendothelial system involvement occurs. Cherry red macula and subretinal white lesions can be observed in patients.

In Niemann-Pick disease, there is a halo of light in the macula and this is pathognomonic. Cherry red macula is observed in 50% of the patients (20).

H) Cystinosis

Cystinosis is an autosomal recessive inherited lysosomal storage disease in which the cystine crystals show intracellular accumulation. In cystinosis, there is a disturbance in the transport of cystine from lysosomes. Therefore, cystine accumulates in lysosomes. It has three types, nephropathic, late-onset, and benign. In all subtypes, cystine crystals accumulate in the cornea and conjunctiva, but only changes in the nephropathic type retina are observed. In retinopathy, patchy depigmented areas are observed in the retinal pigment epithelium. Despite the significant change of fundus, there is no decrease in vision (21,22).

I) Mitochondrial Diseases

Diseases in the mitochondrial respiratory chain due to defects. These defects may be due to nuclear DNA or Mitochondrial DNA mutations. Very heterogeneous clinical findings are observed. Multiple organ involvement can be monitored as well as single organ involvement. Generally, association with myopathies is common. Chronic progressive external ophthalmoplegia, NARP (neurogenic muscle weakness, ataxia, retinitis pigmentosa), and MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke), Leber's hereditary optic neuropathy are included in this group. Patients have pigmented retinopathy of varying severity. In the early period, macular retinal pigment epithelium rarely spikes when pigmenting changes are observed. Kearns - Sayre, the syndrome accompanied by cardiomyopathy, has serious ERG disorders and retinopathy (23-25)

TREATMENT

Today, modern medicine aims to analyze pathologies at the molecular level. The development in gene sequence analysis and gene treatments has enabled scientists and clinicians to resolve genetic pathologies to the extent they are. As a result,

gentle retinal treatments have made tremendous progress in a few decades. Discoveries in viral and nonviral gene transport vectors have paved the way for many successful studies. Moreover, the fact that the CRISPR-Cas (clustered regularly interspaced short palindromic repeats) system developed and changed the dominant and recessive alleles increased the therapeutic power of gene therapies. Genetic surgery in the eye involves the delivery of exogenous genetic material to cells with hereditary genetic defects, while genome surgery focuses on the precise modification of endogenous genomes to correct mutant alleles. Giving gene support to sick cells can occur via viral or non-viral vectors. Currently, adenoviruses, adeno-associated viruses (AAVs), and lentiviral vectors represent most of the viral vectors used for gene therapy (26,27). In addition, some groups examined the complete correction of ocular genetic mutations using site-specific nucleases and allowed genome modification with surgical precision (examples are shown in **Figure 1** and ref. 6-13). It should be noted that the regulation of genomes of postmitotic differentiated neurons using homologous recombination is challenging due to the low or incomplete recombination rates and more studies are needed to optimize these rates (13).

CONCLUSION

There is a light of hope for the treatment of these genetic-based diseases that are still complex and difficult to solve. With the small progress we have made, results that are hard to believe are achieved already. However, we have little knowledge and experience in this regard. As we know about the genome and our ability to correct mutations and edit the genome, the treatment methods we have will develop as well. In addition, with genetic regulation, we may have skills such as improvement in night vision and supervision..

ETHICAL DECLARATIONS

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Original Article

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Investigation of relationship between coronary angiography results and neutrophil/lymphocyte ratios of patients with acute coronary syndrome in the emergency department

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ABSTRACT

Purpose: We aimed to identify patients diagnosed with acute coronary syndrome (ACS) in the emergency department and for whom medical treatment was decided during coronary angiography, according to their neutrophil/lymphocyte ratios at the time of admission.

Material and Method: Patients diagnosed with ACS in the emergency department and undergoing coronary angiography (CAG) were included. The patients were divided into two groups as non-ST-segment elevation acute coronary syndrome and ST-segment elevation myocardial infarction. According to their CAG results, the patients in both groups were classified as those who underwent coronary intervention and those who did not. In addition, demographic data such as age and gender, neutrophil/lymphocyte ratio, monocytes, aspartate aminotransferase, and C-reactive protein values of these patients were recorded in the data form. These values were statistically compared between those who decided on a coronary intervention during CAG and those who did not.

Results: A total of 647 patients were included in the study. The patients were divided into 325 patients with non-ST-segment elevation acute coronary syndrome and 322 with ST-segment elevation myocardial infarction. The age range of the patients in both groups was 30 to 93. Monocyte, aspartate aminotransferase, neutrophil/lymphocyte ratio, and gender were significant in the diagnosis process. The diagnosis was the only effective factor in detecting patients for whom a coronary intervention was decided during CAG. Gender, age, neutrophil/lymphocyte ratio, aspartate aminotransferase, C-reactive protein, and monocyte values were insignificant.

Conclusion: Even if some parameters such as monocyte count, N/L ratio, and aspartate aminotransferase in patients diagnosed with ACS in the emergency department are ineffective in predicting the medical treatment decision during CAG, they may help in the clinical decision-making process.

Keywords: Acute coronary syndrome, neutrophil, lymphocyte, monocytes, neutrophil/lymphocyte ratio

INTRODUCTION

Cardiovascular diseases are common and the most important cause of morbidity and mortality globally and in our country (1,2). According to the World Health Organization report, it ranks first among the causes of death worldwide (3).

Coronary artery disease (CAD) is the most common cardiovascular disease (1,3) and occurs as a result of ischemia in myocardial tissue(4). CAD is an inflammatory process that develops due to atherosclerosis (4). Studies have shown that it is associated with white blood cells (5,6). The acute coronary syndrome (ACS) diagnosis, which is important in emergency department admissions, can be overlooked due to the intensity and complexity in emergency departments (7). The low-cost and widely available neutrophil/lymphocyte (N/L) ratio has recently emerged as a marker in cardiac patients (8).

In our study, by retrospectively analyzing the data of patients diagnosed with ACS in the emergency department and who underwent coronary angiography (CAG), we aimed to investigate whether the N/L ratio could be used as an independent parameter in the determination of patients for whom coronary intervention was decided during CAG.

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MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Ethics Committee (Date: 07.01.2021, Decision No: 2020-KAEK-143-22.01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who presented to the emergency department were diagnosed with ACS and undergoing CAG between January 1 and December 31, 2020, were included in the study. The patients were evaluated retrospectively with the data obtained from the hospital information management system. Those younger than 18 and those diagnosed with ACS but who did not undergo CAG were excluded from the study.

Patients included in the study were divided into non-ST-segment elevation ACS (NSTE-ACS) and ST-segment elevation myocardial infarction (STEMI). According to their CAG results, patients in both groups were classified as those who underwent coronary intervention and those who did not. In addition, demographic data such as age and gender and N/L ratio, monocytes, aspartate aminotransferase (AST), and C-reactive protein (CRP) values from blood tests taken at the time of admission to the emergency department were recorded in the data form. These values were statistically compared between those who decided on coronary intervention during CAG and those who did not.

In this study, a binary logistic regression analysis was conducted to define the relationship between the binary outcome variable (dependent variable) and independent variables consisting of both continuous and discrete (categorical) variables (9). Logistic regression, similar to other regression models, enables the development of the model that has the best fit with the least number of independent variables. Since the dependent variable was categorical and the data did not have multiple normal distributions ($p<0.05$), it was deemed appropriate to use this model (10). Analyzes were performed with IBM SPSS 26 software.

The aim here is to estimate the effects of changes in the independent variables on the change in the dependent variable. The study consists of two stages (two models were created). In the first stage, the effect of the parameters considered while diagnosing NSTE-ACS or STEMI was statistically examined. In the second stage, the effect of the parameters checked at the time of admission on the decision of coronary intervention according to CAG was investigated.

RESULTS

A total of 647 patients diagnosed with ACS and undergoing CAG were included in the study. Among the patients, 325 patients were grouped as NSTE-ACS and 322 patients as STEMI. Two hundred seventy-one of the patients in the NSTE-ACS group were decided to have coronary intervention during CAG, while 54 did not have any pathology requiring coronary intervention. On the other hand, 316 of the STEMI group were decided to have coronary intervention during CAG, while there was no pathology requiring coronary intervention in 6. The age range of NSTE-ACS patients was 30 to 88, with a mean age of 63.26 years. On the other hand, the age range of STEMI patients was 30 to 93, with a mean age of 63.89 years.

The categorical variables of the study are given in **Table 1**.

At the first stage, a Binary Logistic Regression analysis was used to investigate the contribution of the medical variables taken into account in the diagnosis process of a total of 647 patients who were examined with the diagnosis of NSTE-ACS (325) or STEMI (322) in the emergency.

The dependent variable was the categorical diagnostic variable, and patients with NSTE-ACS were defined as patients with STEMI. In addition, the categorical independent variables were gender and age, while continuous variables were N/L ratio, monocytes, CRP, and AST.

The method was carried out by choosing the Forward Stepwise LR model. Thus, using the probability ratios, the significant variables in the model were selected step by step, and the nonsignificant variables were removed from the model. Therefore, it was ensured that the software decided which of the six independent variables had a statistically significant effect (explanatory) on the change of the dependent variable, and the best model was selected. The analysis was carried out in 4 steps. The final and best model in step 4 is included here. Information about the model is given in **Table 2**.

In **Table 2**, the independent variables estimated to be effective in determining the diagnosis (NSTE-ACS or STEMI) are listed in the first column. Accordingly, age and CRP were not found to be effective in diagnosis according to the model.

Table 2. Binary Logistic Regression Model for determining the diagnosis: Forward Stepwise (Likelihood Ratio)

Variables	B	S.H.	Wald	S.D.	p	Exp(B)	Confidence limits at 95% confidence interval for Exp(B)	
							Lower	Upper
N/L	0.081	0.022	13.410	1	0.000**	1.085	1.039	1.133
Gender (woman)	0.584	0.192	9.228	1	0.002**	1.793	1.230	2.614
Monocytes	0.623	0.257	5.894	1	0.015*	1.865	1.128	3.086
Ast	0.005	0.002	5.469	1	0.019*	1.005	1.001	1.009
Constant	-1.503	0.275	29.917	1	0.000**	0.222		

* (significant at $p<0.05$ significance level), ** (significant at $p<0.01$ significance level)

Table 1:The categorical variables of the study

Gender	DIAGNOSIS					
	NSTE-ACS			STEMI		
	Coronary intervention was decided	Coronary intervention was not decided	Total	Coronary intervention was decided	Coronary intervention was not decided	Total
Female	77	23	100	62	1	63
Male	194	31	225	254	5	259
Total	271	54	325	316	6	322

When the p values in the sixth column are examined, it is clear that the effects of monocytes and AST variables on the model were significant at 0.05 ($p<0.05$), while the effects of N/L ratio and gender variables on the model were significant at 0.01 ($p<0.01$).

The B coefficients in the second column are the numbers by which the variables in the model equation are multiplied. No matter the variable value, it affects the result by multiplying these numbers while determining the diagnosis. It is seen that the sign of all B coefficients in the table was positive. In other words, the higher the value of the variables is, the higher the probability of the diagnosis being STEMI is. The situation is similar in gender, which is a categorical variable. According to the model, if the N/L ratio, monocytes, and AST values increase similarly, the probability of having STEMI increases if the patient is male.

While the seventh column contains the Exp(B) values, the eighth and ninth columns contain the lower and upper limits of the Exp(B) calculated at the 95% confidence interval. When the Exp(B) values are examined, it is possible to say that if the N/L ratio increases by 1 unit, the probability of having STEMI will increase 1.085 times on average. Similarly, due to a 1 unit increase in monocytes and AST values, the probability of having STEMI is likely to increase 1.865 times and 1.005 times, respectively. A similar conclusion can be reached for the gender variable. The probability of a male patient having STEMI is, on average, 1,793 times higher than that of a female.

In the second stage of the study, the changes in the parameters were investigated depending on the diagnosis and whether a coronary intervention was decided in patients who underwent CAG. For this purpose, a binary logistic regression analysis was used to examine the contribution of the medical variables taken into account in the process of deciding whether or not to take a coronary intervention during CAG in a total of 647 patients who were examined with the diagnosis of NSTE-ACS (325) or STEMI (322) in the emergency presentions.

The dependent variable was the categorical procedural variable, and it was defined as the patients who were given a coronary intervention during CAG and those who were not. Among the independent variables, the diagnosis (NSTE-ACS and STEMI) and gender (Female, Male) were categorical, while age, N/L ratio, monocytes, CRP, and AST were continuous variables.

The method was carried out via the Forward Stepwise LR model. Thus, we aimed to add the effective variables in the model using the probability ratios, and the ineffective variables were removed from the model. Therefore, it was ensured that the software decided which of the seven independent variables had a statistically significant effect (explanatory) on the change of the dependent variable, and the best model was selected. Thus, analysis was carried out in one step. Information about the model is given in **Table 3**.

In **Table 3**, the independent variable that is estimated to be effective in determining whether to take action or not is in the first column. According to the model, the only factor that is effective in treating the patient is the diagnosis. Other factors do not affect the model.

When the p values in the sixth column are examined, it is clear that the effect of the diagnosis variable on the model is significant at the 0.01 ($p<0.01$) significance level.

The second column contains the coefficient B. This value is the number by which the variable is multiplied in the model equation. No matter the variable's value, the diagnostic value is multiplied by this number, affecting the result. Therefore, the negative sign of the B coefficient of the diagnosis variable indicates that the probability of performing a medical procedure increases when the diagnosis is STEMI.

When the Exp(B) values are examined, the probability of performing a coronary intervention when the patient is diagnosed with STEMI according to the model is determined as 0.095 times higher than that of the patients diagnosed with NSTE-AKS.

DISCUSSION

ACS is divided into three groups as unstable angina, NSTE-ACS, and STEMI. ACS diagnosis is made according to clinical features, electrocardiogram (ECG) findings, and biochemical parameters (11). CAD accounts for more than half of all cardiovascular diseases in people under the age of 75. The prevalence of CAD in the United States is estimated to be 6.4% (12). Therefore, immediate evaluation of patients with suspected ACS is essential to prevent potentially fatal clinical outcomes and reduce ongoing ischemia (13). While patients diagnosed with STEMI undergo immediate reperfusion therapy, patients diagnosed with NSTE-ACS receive early or delayed invasive treatment (14,15).

In the guidelines, percutaneous coronary intervention (PCI) is recommended for patients diagnosed with STEMI within 120 minutes, and fibrinolytic therapy is recommended if PCI cannot be performed within this period (14). Since cellular dysfunction begins very rapidly due to cellular ischemia, early and accurate diagnosis of patients who will undergo PCI is essential. Furthermore, with the advancing technology and high-sensitivity troponin, it aims further to shorten these periods (16,17).

Rapid recognition and immediate treatment of ACS patients are vital. Although the most important symptom is chest pain, it has been shown that some patients may have ACS without chest pain. Studies have shown that female patients are more likely to present without chest pain than males. In-hospital mortality is higher and worse, especially in young female patients diagnosed with STEMI (18-20). High mortality rates and poor prognosis have been found to decrease with age (19,20). In the study by Haaf ME et al., the number of female

Table 3: Binary Logistic Regression Model for determining the diagnosis: Forward Stepwise (Likelihood Ratio)

Variables	B	S.H.	Wald	S.D.	p	Exp(B)	Limits at 95% confidence interval for Exp(B)	
							Lower	Upper
Diagnosis (NSTE-AKS)	-2.351	0.438	28.778	1	0.000**	0.095	0.040	0.225
Constant	-1.613	0.149	117.171	1	0.000**	0.199		

*significant at α=0,05significance level, **significant at α=0,01significance level, -2Log likelihood=352,009

patients requiring CAG was less than males (20). In these studies, the rate of males was found to be higher in patients diagnosed with ACS (18-20). In our study, we found that the rate of males was approximately three times higher than that of females and that male patients were more likely to have STEMI than females. However, we determined that gender was not important to predict patients who required medical procedures during CAG at presentation time.

It has been shown that inflammation is involved in the pathophysiology of CAD, initiation, progression, and rupture of atherosclerotic plaque, and ultimately in thrombotic complications of plaques (21-23). Neutrophils are one of the most important components of the inflammatory process in atherosclerosis. Neutrophil-associated oxygen radicals and some enzymes have been associated with the atherosclerotic process. In addition, it has been found that the decreased lymphocyte level associated with ACS suppresses the immune response, and the suppressed immune response is associated with an increased risk of future infarct tissue area and atherosclerotic plaque rupture (24-26). It has been demonstrated that leukocytosis and high N/L ratio are associated with increased cardiovascular mortality and have prognostic value when evaluating adverse clinical outcomes (27,28). The study by Kalay et al. showed that the N/L ratio is associated with the progression of coronary atherosclerosis (29). In the study of Wang et al., the N/L ratio was a predictor of mortality and cardiovascular events in patients who underwent CAG or cardiac revascularization (30). Furthermore, the N/L ratio was strongly associated with stent thrombosis (29-31). Our study found that the effect of the N/L ratio in the diagnosis process was significant at the 0.01 ($p<0.01$) significance level. According to this result, we think that the N/L ratio can be used as an additional marker in ACS diagnosis. However, medical procedures are not performed for every ACS patient admitted to the catheter laboratory. Our study did not significantly determine patients who underwent medical procedures during CAG, which is our leading target group, according to the N/L ratio at the time of admission. It is seen that the only effective factor in this patient group is diagnosis. According to this result, accurate diagnosis of ACS patients is important for the treatment process.

While many blood cells such as neutrophils, lymphocytes, and monocytes are involved in the inflammation process of the coronary arteries, blood parameters such as CRP, which is an acute-phase reactant, begin to increase when an acute event develops (32). In various studies, a strong correlation was found between increased CRP level with atherosclerosis, coronary microvascular dysfunction, and coronary thrombus burden (33-35). In addition, it has been suggested that there is a relationship between the number of monocytes and plaque progression in cardiac events, and it has been found that monocyte levels are significantly higher in patients with ACS (36,37). Unlike these studies, in our study, since the contribution of the examined parameters to the diagnosis process and the ability to predict the patients requiring medical procedure during CAG according to the results at the time of admission were evaluated, it was found that CRP was ineffective in recognizing patients who required medical procedure both during the diagnosis process and during CAG. However, although the value of monocytes at admission is insufficient in recognizing patients requiring medical procedures during CAG, it is significant in the diagnosis process.

Study Limitations

Our study had several limitations. It was a single-center study with all the constraints inherent in a retrospective analysis. The diagnosis of ACS was based on documentation from the treating physicians. In addition, CAG could not be performed in all patients diagnosed with the acute coronary syndrome.

CONCLUSION

ACS is a life-threatening disease that affects many people. Therefore, recognition and effective treatment of ACS is crucial. Although some parameters such as leukocyte count, neutrophil count, monocyte count, and N/L ratio obtained from complete blood counts that are cheap and fast in patients followed up in the emergency departments due to ACS are ineffective in predicting the decision of medical procedure during CAG, it can help in the clinical decision-making process and predict the prognosis and mortality. However, we think that the parameters evaluated in our study were ineffective in predicting the medical procedure decision during CAG may be because we only included patients who underwent CAG. Therefore, further studies are needed to define the role of the N/L ratio in patients undergoing CAG.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Ethics Committee (Date: 07.01.2021, Decision No: 2020-KAEK-143-22.01).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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Original Article

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Evaluation of the approach to hemodialysis vascular access during the pandemic period

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ABSTRACT

Objective: During the pandemic, some surgeries were postponed due to the large number of patients admitted by hospitals. It was tried to shorten the hospitalization period of some patients. Hemodialysis patients who had to come to the hospital frequently were also affected by this situation. Physicians working during the pandemic period prefer to use less invasive techniques. In this study, it was aimed to investigate whether there is a change in the choice of vascular access used for hemodialysis in this period.

Materıal and Method: In this study, 552 patients who were treated for hemodialysis vascular access in the cardiovascular surgery clinic of Kastamonu University Training and Research Hospital between March 2019 and 2021 were retrospectively analyzed. The patients were divided into two groups as pre-pandemic (Group 1) and pandemic (Group 2). Patients in Group 1 and Group 2 needed high-flow vascular access to perform hemodialysis. For this purpose, 2 techniques are frequently used, the first being arteriovenous fistula(AVF) and the other permanent hemodialysis catheter insertion. The distribution of these techniques used in patients was examined.

Results: In our study, we found that before the pandemic between March 2019-2020, 109 patients had AVF and 193 patients had a permanent tunneled catheter. Between March 2020- 2021, which started with the pandemic process, we found that AVF was opened in 74 patients and a permanent tunnel catheter was placed in 176 patients.

Conclusion: Uremic patients who need hemodialysis should not be affected by the pandemic problem and the most permanent procedures should be applied for these patients. Like all vascular patients, dialysis patients should not become secondary afflictions of Covid-19.

Keywords: Hemodialysis, pandemic, vascular access, arteriovenous fistula, permanent hemodialysis catheter

INTRODUCTION

Chronic Kidney Failure is a common and important public health problem in the world and in our country. End-stage kidney disease is increasing rapidly all over the world and affects 75-350 million people in developed countries. An average of 15000 end-stage renal disease is diagnosed annually in Turkey (1).

Hemodialysis, peritoneal dialysis or kidney transplantation can be performed in patients with end-stage renal disease (2). Permanent or temporary vascular access routes are prepared in order to ensure adequate blood flow during the application in patients who are decided on hemodialysis. (3). These vascular access routes prepared for the purpose of entering hemodialysis and their type, the complications they cause both during and after the opening of the way are one of the most important reasons affecting mortality, morbidity and health expenditures in these patients who require end-stage hemodialysis. Although it is known that the best vascular access is the AVF, the rate of AVF use is still very low in many countries. In addition, differences can be observed between countries in terms of the use of vascular access (4).

After the Covid 19 pandemic affected the whole world, it reached our country over time. As surgeons, we have entered a period in which elective surgeries are postponed in this process, which is considered a pandemic in our country as of March 2019. In our study, we wanted to compare how we approached the cardiovascular surgery clinic to opening a vascular access to end-stage patients with chronic renal failure, which we consider as a special patient group, and how the process affected our surgical approach to these patients compared to the one year period before the pandemic.

MATERIAL AND METHOD

The study was carried out with the permission of Kastamonu University Ethics Committee (Date: 17.11.2021, Decision no: 2020-KAEK-143-95). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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In this study, 552 patients who were treated for hemodialysis vascular access in the cardiovascular surgery clinic of Kastamonu Training and Research Hospital between March 2019 and 2021 were retrospectively analyzed. The patients were divided into two groups as pre-pandemic (Group 1) and pandemic (Group 2). Patients in Group 1 and Group 2 needed high-flow vascular access to perform hemodialysis. For this purpose, 2 techniques are frequently used, the first being arteriovenous fistula and the other permanent hemodialysis catheter insertion. The distribution of these techniques used in patients was examined. Adult patients older than 18 years of age were included in the study. Patients in need of graft vessels and pediatric patients were not included in the study.

Statistical Analysis

In this study, the distribution of data between groups was analyzed as a percentage.

RESULTS

As a result, 15% decrease was observed in the number of patients in Group 2 who had vascular access due to chronic renal failure compared to Group 1.When the patients in Group 1 and Group 2 were compared in terms of arteriovenous fistula, 31% reduction in Group 2 was observed. However, a slight difference of 6% was detected between each 2 years in the insertion of permanent tunneled catheters in these patient groups (**Table 1**).

Table 1: Distribution of patients to groups according to preferred hemodialysis vascular accesses

	Group 1 (n: Patient Number)	Group 2 (n: Patient Number)	% (%: Percentage of difference between the years 2019-2020)
Number of patients admitted to the study	302	256	-15
Arteriovenous Fistula	109	75	-31
Permanent Catheters	193	181	-6

DISCUSSION

Studies in China, Italy, the United Kingdom, and the United States (New York and southern California) have shown that end-stage dialysis patients with chronic renal failure who contract Covid-19 experience a higher mortality rate and more severe illness than the general population (5).

Hemodialysis is the leading extracorporeal treatment. (6) End-stage renal disease patients receiving maintenance dialysis have an average age of 65 years and typically have multiple medical co-morbid conditions, including diabetes, obesity, and impaired immunity from uremia. For this reason, this group of patients is more prone to COVID-19 and has the risk of transmitting the disease with more severe and fatal consequences. If this group of patients resides especially in big cities, the risk of contracting the disease may increase even more because they are socio-economically more disadvantaged than the general population. In addition, the risk factors for both themselves and their relatives increase in these patients due to the fact that an effective physical distance cannot be maintained due to the need for public transportation to the hemodialysis centers and that they often come together in dialysis centers (7).

The biggest concern in the world at the beginning of the pandemic was the behavior of COVID-19 in hemodialysis (HD) units, because social isolation would not be applicable to this population and these patients were extremely susceptible to the complications of the disease. Therefore, a number of other special measures were introduced for dialysis centers (8). In addition, in this process, it is recommended by some authors to provide the most suitable sterile conditions to open a hemodialysis route in patients, to open vascular access routes in the operating room if possible, to approach patients with fully equipped protective personal equipment during the surgical procedure (9).

Some authors recommend that more permanent pathways should be made and used in end-stage renal disease patients who will enter hemodialysis dialysis for the first time during the pandemic process. Patients with short-term temporary catheters represent the most critical cases in terms of vascular access; a tunneled catheter or fistula should be preferred for the transition to a permanent route; because these accesses require fewer replacement procedures to maintain patency, they result in fewer hospital visits and less risk of infection for each permanent procedure, making an arteriovenous fistula (AVF) is not an elective procedure. In addition, these authors reported that especially AVF opening is not an elective procedure and should not be postponed due to the uncertainty of the pandemic process (10).

As in the whole population, negative reactions that we have never seen before are witnessed in hemodialysis patients against this epidemic. Patients may refuse to come to the hospital and receive the repair of thrombosed arteriovenous grafts, correction of large pseudoaneurysms, or even transplantation that has been expected for several months in order not to be contaminated with the Covid-19 virus. Because these patients are aware that they are the most vulnerable group against Covid-19. However, a well-functioning fistula and an indwelling catheter in these patients can overcome this fear (11).

Surgeons who set up the vascular route for hemodialysis should lead to lower hospitalization rates with optimal outcomes. Both nephrologists and surgeons must convince these patients that even in this time of global human threat, healthcare delivery will be safe and of the best quality. The strategy for establishing and maintaining a vascular pathway in patients with kidney disease should be undertaken in line with the latest universal recommendations, in a designated sterile operating room environment with adequate protection for medical personnel and patients. What we need right now is a situation that requires a sterile operating environment, a short hospital stay, the least possible morbidity rates, and a one-time solution to the problem.

With this thought in mind, we continued our patients with chronic kidney failure in the first year after the pandemic and who were scheduled for hemodialysis due to end-stage kidney disease, without significantly reducing the ways that should be permanent in the operating room conditions in accordance with the pandemic rules, compared to one year before the pandemic.

CONCLUSION

Uremic patients who need hemodialysis should not be affected by the pandemic problem and the most permanent procedures should be applied for these patients. Like all vascular patients, dialysis patients should not become secondary afflictions of Covid-19..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kastamonu University Ethics Committee (Date: 17.11.2021, Decision no: 2020-KAEK-143-95).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

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An examination of sex hormone levels in epilepsy patients taking antiepileptic treatment

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ABSTRACT

Aim: Reproductive adverse events may be observed in patients with epilepsy associated with antiepileptic drugs. This study aimed to evaluate changes in sex hormone levels in patients receiving antiepileptic treatment as monotherapy and polytherapy.

Material and Method: In this case-control study, the sex hormone levels and free androgen indexes were evaluated in 83 patients and 40 controls. In the hormone evaluations, measurements were performed for dehydroepiandrosterone sulfate, sex hormone-binding globulin, follicle-stimulating hormone, luteinizing hormone, total and free testosterone, prolactin and estradiol levels.

Results: A total of 83 patients (42 males, 41 females) with a mean age of 28±7.2 years and a control group of 40 healthy subjects (14 males, 26 females) with a mean age of 33±8.7 years were included. In the patient group, 45 were receiving monotherapy and 38 polytherapy, 13 (15.7%) patients had focal onset seizures, 68 (81.9%) had generalized onset seizure and 2 (2.4%) had seizure type of unknown origin. In the males of the study group, no difference was determined in the hormone levels. In the females of the study group, the free androgen index was determined to be significantly low in the carbamazepine group compared to the control group (p=0.04) and the sex hormone-binding globulin values were significantly high (p=0.01). In males, a significant positive correlation was determined between serum carbamazepine and follicle-stimulating hormone (p=0.046) and prolactin (p=0.035) and a significant negative correlation was determined with the free androgen index (p=0.032). In females, a statistically significant positive correlation was determined between carbamazepine and prolactin (p=0.036).

Conclusion: The use of antiepileptic drugs creates changes in the sex hormone levels in males, and associated reproductive side-effects may be seen. In the management of patients with epilepsy, an awareness of these side-effects and individual evaluation could have a positive effect on treatment compliance and patient satisfaction.

Keywords: Epilepsy, antiepileptic drugs, sex hormones

INTRODUCTION

Epilepsy is a chronic neurological disease that affects approximately 1% of the general population. While monotherapy is sufficient in approximately 70% of the patients, 30% have resistant epilepsy (1). It is known that the incidence of reproductive hormone disorders is higher in patients with epilepsy compared to the normal population. In patients with epilepsy, sexual dysfunction has been found in 30-60% of men and 14-50% of women (2-4). Studies have shown that one of the important side effects of antiepileptic treatment is sexual dysfunction (5,6). This side effect can affect both genders and cause negative effects due to psycho-physiological changes in the sexual response cycle. Polycystic ovary syndrome, hypothalamic amenorrhea or hyperprolactinemia may be observed in women using AEDs (7,8). Among the side effects observed in men are decreased libido, erectile dysfunction, and lack of sexual satisfaction and sperm anomalies (9,10). In the light of this information, we evaluated the possible effects of treatment on sex hormones in patients with epilepsy who received antiepileptic treatment in the form of monotherapy and polytherapy.

MATERIAL AND METHOD

The study was carried out with the permission of Non-Drug Clinical Research Ethics Committee of Istanbul Haseki Training and Research Hospital (Date: 20.08.2014, Decision No: 138). An informed consent was obtained from all participants of the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In the present case-control study, a total of 83 patients who received antiepileptic treatment in the form of monotherapy (n=45) and polytherapy (n=38) in our hospital's Neurology Clinic and 40 healthy control subjects had dehydroepiandrosterone sulfate (DHEA-S), sex hormone-

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binding globulin (SHBG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total and free testosterone, prolactin and estradiol levels and free androgen index (FAI) (total testosterone/SHBG) were evaluated.

Patients between the ages of 18-45, diagnosed with definite epilepsy with clinical and EEG findings, using the same antiepileptic drug or drugs for at least the last six months and with serum antiepileptic drug levels at therapeutic level were included in our study. Patients with a history of seizures 48-72 hours before blood collection, patients with genitourinary and endocrinological diseases, a history of regular use of any drug other than the antiepileptic drug used, those with antiepileptic drug serum levels outside the therapeutic limits, patients with hypo- or hyper-albuminemia, those with hypo- or hyperglycemia, those with abnormal liver enzyme function tests, those with known genitourinary, endocrinological diseases (known pituitary adenoma, polycystic ovary syndrome, menstrual irregularity, etc.), those with a history of acute or chronic infection, chronic liver and kidney disease or malignancy Patients with known alcohol and substance abuse were excluded.

Epileptic seizure types of the patients were grouped according to the 2017 classification of the International League against Epilepsy. Hormone and drug blood levels of the participants were measured from the blood samples taken between 08:00 and 10:00 before the morning drug dose after fasting overnight. Blood test was taken one week after the end of menstrual bleeding in women in the patient and control groups.

In biochemical evaluations, free testosterone level using Diametra brand kits in Biotek ELx808 device (BioTek Instruments, Winooski, VA, USA) with enzyme-linked immunosorbent assay method, SHBG level using Beckman Coulter brand kits with immunoradiometric assay method in Stratec SR300 device (STRATEC SE, Birkenfeld, Germany), other hormones using Beckman Coulter brand kits Beckman Coulter UniCel DxI 800 (Beckman Coulter Diagnostics, CA, USA). Drug levels were studied with the fluorescence polarization immunoassay method on the COBAS INTEGRA 400 plus analyzer (Roche Diagnostics, Basel, Switzerland) using Roche branded kits.

Free testosterone level using Diametra brand kits in Biotek ELx808 device (BioTek Instruments, Winooski, VA, USA) with enzyme-linked immunusorbent assay method, SHBG level using Beckman Coulter brand kits with immunoradiometric assay method in Stratec SR300 device (STRATEC SE, Birkenfeld, Germany) other hormones in Beckman Coulter UniCel DxI 800 (Beckman Coulter Diagnostics, CA, USA) using Beckman Coulter brand kits. With the immunoassay method, drug levels were studied with the fluorescence polarization immunoassay method on the COBAS INTEGRA 400 plus analyzer (Roche Diagnostics, Basel, Switzerland) using Roche branded kits.

Statistical Analysis

Descriptive statistics of the study; number and percentage for categorical variables, mean and standard deviation for numerical variables were given. Comparisons of numerical variables in two independent groups were made with the Mann-Whitney U test, and comparisons of more than two groups were made with the Kruskal-Wallis test. Subgroup comparisons were made with the Mann-Whitney U test and interpreted with Bonferroni correction. The ratios of categorical variables between groups were analyzed using the Chi-square test. Relationships between numerical variables were analyzed using Spearman correlation analysis. All statistical analyzes of the study were performed with the Statistical Package for the Social Sciences for Windows (version 15.0, SPSS., Inc., Chicago, IL, USA) and at a significance level of $p<0.05$.

RESULTS

In the study, the data of 83 cases (male/female: 42/41) with a mean age of 28±7.2 years and 40 healthy controls (male/female: 14/26) with a mean age of 33±8.7 years were evaluated. Forty-five of the patients were receiving monotherapy (male/female 16/29) and 38 polytherapy (male/female, 26/12). Of the patients, 13 had focal onset (15.7%), 68 had a generalized onset (81.9%), and two had an unknown onset of epileptic seizures (2.4%). The demographic findings of the patients are shown in Table 1, and the AEDs used in the monotherapy and polytherapy groups are shown in Table 2.

Table 2. Distribution of the treatments the patients received

	n (%)	Number of males	Number of females
Monotherapy			
LTG	8 (9.6)	-	8
LEV	9 (10.8)	3	6
CBZ	13 (15.7)	4	9
VPA	15 (18.1)	9	6
Total	45 (54.2)		
Polytherapy			
LTG-CBZ	4 (4.8)	3	1
LTG-LEV	4 (4.8)	3	1
LTG-VPA	3 (3.6)	1	2
CBZ-LEV	11 (13.3)	8	3
CBZ-VPA	5 (6)	4	1
LEV-VPA	11 (13.3)	7	4
Total	38 (45.8)		

LTG, lamotrigine; LEV, levetiracetam; CBZ, carbamazepine; VPA, valproic acid.

Table 1. Demographic findings of the patients

	CBZ	LTG	LEV	VPA	Polytherapy	p
Age, year, mean±SD	26.2±6.8	24.4±6.3	26.9±8.0	23.8±5.3	30.7±7.9	0.020
Sex, n (%)	4 (30.8)	0 (0.0)	3 (33.3)	9 (60.0)	26 (68.4)	0.001
Male	9 (69.2)	8 (100)	6 (66.7)	6 (40.0)	12 (31.6)	
Female						
Age at first seizure, year, mean±SD	15.1±7.9	14.4±10.1	16.9±13.0	13.9±6.2	17.9±10.2	0.634
Epilepsy, year, mean±SD	11.1±7.1	9.9±6.0	9.9±11.9	9.9±6.2	12.7±8.3	0.588
Epilepsy type, n (%)						
Focal onset	10 (76.9)	6 (75.0)	9 (100)	13 (86.7)	30 (78.9)	0.764
Generalized onset	2 (15.4)	2 (25.0)	0 (0.0)	2 (13.3)	7 (18.4)	
Seizure onset unknown	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.6)	

CBZ, carbamazepine; LTG, lamotrigine; LEV, levetiracetam; VPA, valproic acid; SD, standard deviation.

The mean age of the group receiving monotherapy was statistically significantly lower than that of the polytherapy group and the control group (p=0.001, p<0.001). Male gender ratio was high in the polytherapy group. There was no statistically significant difference between the age of first seizures, epilepsy years averages, epilepsy types in the monotherapy and polytherapy groups (p=0.177, p=0.168, p=0.775). The distribution of the treatments used by the patients is summarized in Table 2.

There was no statistically significant difference in the mean hormone levels of the groups in men.

In women using carbamazepine (CBZ), it was found that the FAI value was significantly lower (p=0.04) and the SHBG values were significantly higher than the control group (p=0.01) compared to the control group (Table 3).

Serum CBZ levels were positively correlated with FSH (p=0.046) and prolactin (p=0.035) in men, negatively with FAI (p=0.032), and positively with prolactin (p=0.036) in women (Table 4).

Considering the duration of antiepileptic drug use, it was observed that the level of estradiol increased significantly in female patients using lamotrigine (LTG) (p=0.003). There was no statistically significant relationship between drug use duration and hormone levels in men (Table 5).

Table 3. Hormonal evaluation results in study groups

	CBZ Mean±SD	LTG Mean±SD	LEV Mean±SD	VPA Mean±SD	Polytherapy Mean±SD	Control group Mean±SD	p
Male							
FSH	5.2±3.4	-	2.8±1.2	4.6±2.1	5.9±4.0	5.7±2.2	0.24
LH	3.8±0.9	-	4.2±1.7	4.4±1.4	5.4±2.7	5.4±2.0	0.49
Estradiol	26.0±12.6	-	30.0±12.8	23.6±15.9	24.3±15.9	24.1±12.8	0.95
Progesterone	0.46±0.07	-	0.56±0.33	0.56±0.40	0.72±0.61	0.76±0.44	0.78
Total testosterone	340.3±121.5	-	365.7±82.4	411.0±102.7	405.3±155.9	408.4±119.3	0.89
FAI	40.23±18.31	-	71.04±46.35	63.86±38.50	51.90±31.36	53.26±20.74	0.60
DHEA-S	187.2±72.1	-	293.4±90.0	252.0±128.5	230.9±146.1	212.8±108.2	0.66
Prolactin	8.0±2.7	-	10.7±5.6	8.7±4,0	8.3±3.7	10.4±4.8	0.67
SHBG	31.3±10.5	-	22.1±9.8	31.0±18.5	37.4±24.0	30.6±14.7	0.83
Female							
FSH	5.6±4.2	4.7±2.4	9.8±10.4	6.5±2.2	6.4±3.6	8.0±8.0	0.51
LH	8.1±6.7	4.3±3.4	7.9±7.1	8.5±10.4	10.9±13.1	11,9±10.7	0.31
Estradiol	150.7±90.5	80.8±44.9	105.8±78.6	65.0±54.3	111.5±114.3	122.9±108.5	0.47
Progesterone	5.2±5.3	10.7±13.4	3.8±7.1	2.6±4.4	2.7±4.1	2.9±5.2	0.21
Total testosterone	36.9±15.2	27.1±14.2	39.7±13.4	46.3±17.0	43.3±15.2	44.1±17.1	0.20
FAI	1.36±0.95*	2.42±2.55	2.26±0.90	4.12±4.03	2.16±1.17	3.98±3.25	0.04
DHEA-S	159.9±92.6	147.3±75.9	193.3±81.2	181.7±93.3	165.1±77.4	208.7±104.7	0.52
Prolactin	13.8±5.6	32.6±53.0	11.7±4.3	12.2±6.8	15.6±12.2	15.0±8.3	0.84
SHBG	140.3±129.3*	79.5±97.5	64.0±15.2	81.3±62.5	108.0±109.4	55.6±40.1	0.01

* significantly different as compared with the control group. CBZ, carbamazepine; LTG, lamotrigine; LEV, levetiracetam; VPA; valproic acid; FSH, follicle-stimulating hormone; LH, luteinizing hormone; FAI, free androgen index; DHEA-S, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin. SD, standard deviation.

Table 4. Relationships between drug serum level and hormonal parameters

		FSH	LH	Estradiol	Progesterone	Total testosterone	FAI	DHEA-S	Prolactin	SHBG
Male										
CBZ serum level	rho	0.46	-0.17	-0.27	-0.28	-0.26	-0.49	0.15	0.49	0.19
	p	0.05	0.48	0.26	0.25	0.29	0.03	0.54	0.04	0.44
VPA serum level	rho	0.23	0.03	0.21	0.00	-0.13	-0.17	0.17	-0.44	0.03
	p	0.34	0.92	0.39	0.99	0.59	0.49	0.50	0.06	0.91
Female										
CBZ serum level	rho	-0.27	0.57	0.17	0.12	0.10	-0.02	0.07	0.70	-0.10
	p	0.49	0.11	0.67	0.77	0.80	0.97	0.87	0.04	0.80
VPA serum level	rho	0.49	0.77	-0.37	-0.26	-0.14	-0.26	-0.60	0.43	0.14
	p	0.33	0.07	0.47	0.62	0.79	0.62	0.21	0.40	0.79

FSH, follicle-stimulating hormone; LH, luteinizing hormone; FAI, free androgen index; DHEA-S, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin; CBZ, carbamazepine; VPA, valproic acid.

Table 5. Antiepileptic drug use times

		FSH	LH	Estradiol	Progesterone	Total testosterone	FAI	DHEA-S	Prolactin	SHBG
Female										
Duration of CBZ treatment	rho	0.251	-0.218	-0.084	-0.209	-0.126	0.033	0.025	0.067	-0.008
	p	0.515	0.574	0.831	0.589	0.748	0.932	0.949	0.864	0.983
	n	9	9	9	9	9	9	9	9	8
Duration of LTG treatment	rho	0.458	0.639	0.892	0.410	-0.398	-0.277	-0.036	-0.446	0.386
	p	0.254	0.088	0.003	0.313	0.329	0.506	0.932	0.268	0.346
	n	8	8	8	8	8	8	8	8	8
Duration of LEV treatment	rho	-0.029	-0.314	0.544	-0.029	0.543	0.143	-0.371	-0.143	0.829
	p	0.957	0.086	0.872	0.957	0.266	0.787	0.468	0.787	0.042
	n	6	6	6	6	6	6	6	6	
Duration of VPA treatment	rho	0.314	0.257	0.371	-0.371	-0.200	-0.086	-0.543	-0.314	0.143
	p	0.544	0.623	0.468	0.468	0.704	0.872	0.266	0.544	0.787
	n	6	6	6	6	6	6	6	6	6

FSH, follicle-stimulating hormone; LH, luteinizing hormone; FAI, free androgen index; DHEA-S, dehydroepiandrosterone sulfate; SHBG, sex hormone-binding globulin; CBZ, carbamazepine; LTG, lamotrigine; LEV, levetiracetam; VPA, valproic acid.

DISCUSSION

The effects of epilepsy on reproductive and endocrine functions have been studied by many researchers since the report of Gastaut and Collomb's 36-disease series (11) in terms of decreases in sexual activity and autoerotic behaviors in 1954. While sexual dysfunction was not found in epileptic patients under treatment in some studies (12), it was shown in some large meta-analysis studies that epilepsy affected sexual functions (13). In the experimental study of Edwards et al. (14), it was shown that sexual dysfunction may be due to epilepsy itself, independent of AEDs. There are also studies suggesting that sexual dysfunction and reproductive hormone disorders are more pronounced in epileptic patients, especially those with complex partial seizures (15-17). The relationship between focal-onset seizures and hippocampus and amygdala atrophy was emphasized as one of the main reasons for this (18,19). Therefore, it is known that sexual dysfunction can be seen in epilepsy, especially due to the damage of temporal structures. On the other hand, endocrine dysfunction in epilepsy can be seen as a side effect due to chronic use of AEDs. AEDs can lead to endocrine dysfunction by changing synthesis, metabolism and bioavailability of sex steroid hormones. In addition, drug-drug interaction between AEDs an also result in endocrine disorders. Another factor resulting in sexual disorders in epilepsy is speculated as the effects of enzyme-inducing AEDs on the microsomal enzyme system, which increases sexual hormone metabolism. The effective mechanism of action that AEDs exerts their effects on hormone metabolism is through stimulation or inhibition of cytochrome P450 isoenzymes. With the detailed evaluation of the effects of enzyme-inducing AEDs on androgen metabolism in recent years, it has been suggested that the effects of enzyme-inducing AEDs on hormone metabolism may be the basis of the functional and endocrinological disorders seen in patients with epilepsy. It has been reported that antiepileptics in this group can increase total testosterone and SHBG levels and decrease free testosterone and FAI (10,16).

There are studies showing that SHBG levels increase or free testosterone levels decrease in male patients using CBZ. In the studies conducted by Svalheim et al. (20) and Rättyä et al. (21), it was found that SHBG, FSH, LH values were higher and DHEA-S and FAI values were lower in male patients using CBZ compared to the control group; In female patients using CBZ, it has been reported that SHBG levels are high and progesterone levels are lower. In our study, we found similarly higher SHBG in female patients compared to the control group, but we found no change in sex hormone levels in male patients using CBZ (table 2). In the study by Isojärvi et al. (22), SHBG values of male patients who received CBZ treatment for five years were found to be significantly higher and FAI values were found to be lower than controls. In the prospective part of this study, hormone levels of newly diagnosed patients who were started CBZ were measured before treatment, in the first and fifth years of treatment, and it was observed that SHBG levels progressively increased during CBZ treatment, but testosterone levels did not change, so there was a progressive decrease in FAI (22). Although this effect of CBZ was seen in the first year of treatment, it was stated that it became more evident in the fifth year, and as a result, CBZ caused premature aging in the reproductive system (22). In our study, although the average duration of CBZ use was 11 years, no significant relationship was found between hormone levels. When the relationship between CBZ serum level and sex hormones was examined in our study, it was determined that the increase in CBZ serum level caused an increase in prolactin level in men and women, and an increase in FSH and a decrease in FAI in men. It is also suggested that valproic acid (VPA), another antiepileptic commonly used in the treatment of epilepsy, causes menstrual irregularities and hyperandrogenism as well as polycystic ovary syndrome in women (2, 21, 23). In the study by Duncan et al. (24) in 1999, male patients using VPA were compared with the control group, and it was concluded that VPA did not affect hormonal parameters. In the study of Rättyä et al. (21) in 2000, VPA was started in male patients with epilepsy who were newly diagnosed and followed up for three months, and it was found that the patients' FSH and progesterone levels decreased at the end of the first month, and at the end of the third month there was an increase in DHEA-S levels and a decrease in LH level. Rättyä et al. (21) stated that, unlike his previous researchers, VPA increases androgen levels in men, there is a tendency to decrease serum gonadotropins and this result may be related to sexual dysfunction, VPA may not be as innocent as thought in terms of reproductive system. In our study, we did not find any significant changes in the sex hormone levels of male and female patients using VPA. In the study of Røste et al. (10) in 2003, it was found that serum DHEA-S levels increased and LH and FSH levels decreased after long-term use of VPA therapy in male epilepsy patients. In our study, no significant statistical finding was found between the duration of VPA use and VPA blood level and hormonal changes (tables 3 and 4). VPA may also have an effect on testicular androgen synthesis (24,25). It has been reported that male patients using VPA for antiepileptic treatment may develop infertility. In vitro studies have also reported that VPA has direct effects on sperm motility (24). Clinical studies also reveal that VPA can reduce sperm motility, increase morphologically abnormal sperm count and may be associated with decreased testicular volume in epilepsy patients (9,10). In the study conducted by Svalheim et al. (20) in 2009, sex hormones of a total of 216 epilepsy patients treated with LTG, levetiracetam (LEV) and CBZ monotherapy and a healthy control group of 80 people were examined. It was reported that DHEA-S levels were higher and free testosterone levels were lower in female patients treated with LTG compared to the control group (20). In the study conducted by Stephen et al. (26) with 225 patients in 2007, no change was found in the values of testosterone, SHBG, FAI in patients receiving VPA and LTG monotherapy as a result of the one-year follow-up period of male patients who were newly started treatment. In a randomized prospective study conducted by Kwan et al. (27) in 2009, the sex hormones of 81 patients who received VPA and LTG monotherapy were examined at the end of 12 months. While there was no significant change in total testosterone, DHEA-S, LH and FSH levels in female patients, a significant decrease was found in FSH levels in male patients using VPA (27). In our study, no statistically significant change was found in the sex hormone levels of male patients using LTG as monotherapy; however, it was observed that blood estradiol levels increased as the duration of LTG use increased in female patients. In the study by Svalheim et al. 820), although free testosterone levels were found to be slightly lower in the levetiracetam group compared to the healthy control group, it was not statistically significant. This hormone level difference was most likely due to the difference between epilepsy patients and healthy controls, not to a specific drug effect (20). In the study conducted by Taubøll et al.([28) in 2006, it was

emphasized that LEV had no hormonal effect but could have a proapoptotic effect by activating caspase-3. In our study, we found no significant hormonal changes in male and female patients using LEV. We also observed that the duration of LEV use did not make a significant change on hormone levels (table 4). There are not many studies done with polytherapy. Duncan et al. (24) stated in their study that they found the FAI level lower in the patient groups receiving polytherapy compared to the control group. Galimberti et al. (29) found a decrease in DHEA levels and an increase in cortisol levels in female patients who used enzyme-inducing AEDs, but they did not see these changes in antiepileptic areas that did not cause enzyme induction. In their study, they found that the levels of eutrodiol and FAI were lower in women with epilepsy who received polytherapy with enzyme-inducing drugs compared to women who received monotherapy with a single enzyme induction (29]) In our study, when the polytherapy group was compared with all the monotherapy groups and the control group, no significant difference was found in terms of sex hormone levels.

CONCLUSION

In our study, SHBG levels were found to be significantly higher in female patients using CBZ as monotherapy compared to the control group. The FAI value was found to be significantly lower than the control group. It was found that the increase in CBZ blood level caused an increase in prolactin level in men and women, and an increase in FSH and a decrease in FAI in men. In addition, it was found that as the duration of LTG use increased in female patients using LTG, blood estradiol levels increased.

Being aware of reproductive hormone disorders that can be seen during epilepsy treatment and evaluating their possible relationship with the treatment used is very important for both treatment success and treatment compliance and patient satisfaction. In the literature, there are studies that support each other or report opposite results regarding the changes in sex hormone levels in patients with epilepsy. Our study has results that are both compatible with the literature and are not compatible with the literature. Undesirable effects related to reproductive desire should be closely monitored in patients receiving epilepsy treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Non-Drug Clinical Research Ethics Committee of Istanbul Haseki Training and Research Hospital (Date: 20.08.2014, Decision No: 138).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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The correlation of mean platelet volume (MPV) and neutrophil-lymphocyte ratio (NLR) measurements, and the Ishak fibrosis Score in our patients with chronic hepatitis B

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ABSTRACT

Background: The ishak score determined by liver biopsy is the most reliable indicator of fibrosis, but biopsy is an invasive procedure. Numerous noninvasive tests have been investigated to determine the hepatic fibrosis score. We aimed to investigate the relationship between the mean platelet volume (MPV) and neutrophil lymphocyte ratio (NLR) measurements in patients with chronic hepatitis B virus (CHB) infection, and liver fibrosis stage, which was determined by biopsy and ishak score.

Material and Method: CHB patients followed between 2016 and 2020 in our gastroenterology outpatient clinic were included in our study. CHB patients; They were divided into two groups as non-cirrhotic group (ishak fibrosis score in biopsy; F0-F4) and cirrhotic group (F5-F6). Then, 30 healthy control (HC) groups consisting of health personnel who had routine health screenings and blood tests in the same period were formed. MPV, NLR measurements of these two main groups and CHB subgroups and liver biopsy results of CHB patients were evaluated retrospectively, and possible relationships between the groups were investigated.

Results: There was no statistically significant difference between the mean age and gender of the cases in the CHB and HC groups. A total of 54 patients with CHB were identified, of which 13 patients were cirrhotic and 41 patients were non-cirrhotic. MPV measurements were found to be significantly higher in the CHB group than in the SC group (11.15±1.77; 10.02±0.92; p=0.002). While there was no significant difference between NLR measurements, it was found to be higher in the CHB group (1.98±0.81; 1.81±0.69). While there was no significant difference between the cirrhotic and non-cirrhotic subgroups of the CHB group in terms of NLR (1.86±0.68; 2.36±1.04) and MPV (11.09±1.89; 11.35±1.36) measurements, NLR and MPV measurements were higher in the cirrhotic group.

Conclusion: In our study, MPV values were found to be significantly increased in patients in the CHB group compared to the HC group. In addition, although not statistically significant, NLR and MPV measurements were found to be higher in the cirrhotic group than in the non-cirrhotic group. According to our study, it can be thought that with increasing MPV and NLR measurements in HBV patients, there may be an increase in chronicity and ishac fibrosis scores without an invasive procedure such as biopsy.

Keywords: Hepatitis B virus, MPV, NLR, ishak fibrosis score

INTRODUCTION

Hepatitis B virus (HBV) infection is a significant public health concern around the world. HBV is a carcinogen virus that can cause clinical pictures of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). To prevent progression of fibrosis to cirrhosis has great importance (1). Necro-inflammation constitutes a crucial part of liver pathology in hepatitis and cirrhosis. While the liver biopsy is the "gold standard" for assessment of liver fibrosis, it has some disadvantages like invasive technique, sampling error, poor patient compliance, subjective scoring (2). Taking into consideration these restrictions, noninvasive histology predictors are urgently required (3,4). Staging systems such as Knodell, Metavir, and the Ishak staging systems can be used to demonstrate the degree of fibrosis in histopathological examination of the liver biopsy specimens. The Ishak staging system was created by modifying the Knodell system (which does not contain a stage 2) and it has six stages of fibrosis (0-6). The Ishak staging system has not enjoyed the general popularity of the others. Recently, the Ishak staging system is more commonly used in clinical research. Since each Ishak fibrosis stage reflects more scarring compared to the preceding stage, it is assumed by investigators and clinicians that succession from one stage to the next one represents progressively a more

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advanced liver disease (5-7). Investigators continue to seek specific markers used for the evaluation of the progression of the disease and the determination of the staging (the course of inflammation) (8,9). Models that predict fibrosis comprised of a few serum markers, consisting AAR (AST/ALT), PGAA index (prothrombin time g-GT, apolipoprotein A1, aplha 2-macroglobulin), APRI, hyaluronic acid, collagen, and tissue inhibitor of metalloproteinase have been suggested by some studies (10). However, these tests are not cheap and accessible as mean platelet volume(MPV) and neutrophil lymphocyte ratio(NLR) that can be determined only with complete blood count (CBC) tests. NLR and MPV parameters can routinely be detected by CBC analyzers. MPV is also an indicator of platelet function and activation. The inflammation can influence MPV (11). There are clinical studies showing that MPV is an indicator of the risk of cardiovascular disease, cerebrovascular diseases (including stroke), and mortality (12,13). The possible association between MPV and many liver diseases; steatosis, liver cirrhosis, chronic hepatitis, and overall vascular mortality has also been investigated in recent years (14-16). Nevertheless, until today, MPV's role in other liver diseases has not been fully clarified. These liver diseases include HBV infection and there is no direct association with atherosclerosis (17).

NLR value, which can be easily calculated from routinely available data, has been shown in many studies to be an important indicator for inflammation. Neutrophilia is seen in chronic inflammation. On the other hand, lymphopenia is observed in bacterial infection and malnutrition. It has been shown that elevated NLR values predicted the outcomes in various diseases such as cardiac disease, malignancy, and renal failure (18). Some clinical studies performed have shown that elevated NLR values could be associated with the progression of the disease and also higher mortality rate in patients with acute hepatitis, chronic hepatitis, compensated, and decompensated cirrhosis (19-21). If we go further other than chronic HBV (CHB) and cirrhosis, in a study, while the postoperative 5-year disease-free survival of patients undergoing liver transplantation for HCC with pre-transplant NLR≥5 was 30%, the postoperative 5-year disease-free survival of patients undergoing liver transplantation for HCC with pre-transplant NLR<5 was determined to be 60% (22,23). Therefore, this study was performed to evaluate MPV and NLR in HBV-infected patients.

MATERIAL AND METHOD

The study was carried out with the permission Zeynep Kamil Women and Children Diseases Training and Research Hospital Ethics Committee (Date: 22.05.2019, Decision No: EY.FR.22-54). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Design

In our study, 54 patients with CHB followed up in the outpatient gastroenterology clinic of Uskudar State Hospital, Istanbul, Turkey between November 2016 and April 2020 with serum HBsAg (HBV surface antigen) positivity lasting longer than 6 months, undergoing liver biopsy and receiving antiviral therapy (lamivudine, entecavir, tenofovir disoproxil fumarate, tenofovir alafenamid) were determined as a patient group and 30 hospital personnels (physician, nurse, allied health personnel) without the use of the drug, routine blood tests were asked and periodic examinations were performed by workplace doctor were determined as healthy controls (HCs). Previous blood tests (WBC, Hb, PLT, MPV, neutrophil, lymphocyte, NLR, AST, ALT, ALP, GGT, total bilirubin, albumin, INR, AFP) and histopathological features of liver biopsies of The CHB group (the ishak fibrosis scores: F=0-6, Hepatic Activity Index: HAI=0-15) were screened retrospectively through hospital automation system and previous blood tests of the HCs group (WBC, Hb, PLT, MPV, neutrophil, lymphocyte, NLR, AST, ALT) were screened retrospectively through hospital automation system and the control group was constituted. Eight to eleven point nine fluid ounce (fL) was considered to be the normal range for MPV. The gender distribution and the mean age of the HCs group were similar to the CHB group. Comparisons were performed between blood tests including MPV and NLR of the CHB group and The HCs group. Additionally, the CHB group was divided into two groups as non-cirrhotic CHB group (the ishac fibrosis scores: F0-F4) and the cirrhotic CHB group (the ishac fibrosis scores: F5-F6). Comparisons were performed between blood tests including MPV and NLR of these two groups. Fibrosis was graded following the Ishak staging system that uses fibrosis scores ranging between 0 and 6. The scores in this system were defined as follows:

Two (2) points as fibrous enlargement of most portal areas with or without short fibrous septa; 3 points as fibrous expansion of most portal areas with occasional portal-to-portal bridging; 4 points as fibrous expansion of most portal areas with marked bridging (both portal-to-portal and portal-to-center); 5 points as incomplete cirrhosis characterized by prominent bridging and occasional nodules; and a score of 6 as probable or definite cirrhosis (1,4,5,24). Patients under 18 years of age, with all kinds of malignancies (including HCC), with active infections, and with acute or chronic inflammatory disease were excluded from this study.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Kaysville, Utah, USA) program was used for the statistical analysis. During the evaluation of the study data, descriptive statistical methods were used. Conformity of the quantitative data to a normal distribution was tested by using Kolmogorov-Smirnov, Shapiro-Wilk test, and the graphical assessments. The student t-test was used for the intergroup comparisons of quantitative data with normal distribution and Mann Whitney U test was used for the intergroup comparisons of variables without normal distribution. Pearson's Chi-Square test, Fisher-Freeman-Halton Exact test, and Fisher's Exact tests were used regarding the comparisons of qualitative data. Significance was evaluated at a level of $p<0.05$.

RESULTS

The study was conducted on 54 patients with CHB followed by the gastroenterology clinic of our hospital, and 30 HCs cases (30 (35.7%) females, 54 (64.3%) males). The ages of the cases ranged between 24 and 73 years and the mean age was 46.56±11.66 years. While 41 (75.9%) of patients with CHB were non-cirrhotic, 13 (24.1%) of them were determined to be cirrhotic (**Table 1**). There is no significant difference between the mean ages, gender distribution, and neutrophil, hemoglobin, and NLR measurements of patients with CHB and HCs cases ($p>0.05$). AST, ALT and MPV measurements were determined to be significantly higher in the CHB group

than the HCs group (p=0.001, p=0.001, p=0.002; respectively). PLT measurements were determined to be significantly less in the CHB patients than the HCs group (**Table 2**, **Figure 1**). A statistically significant difference was determined between the ages of patients with CHB based on being cirrhotic (p=0.014). The mean age of the cirrhotic group was higher than the non-cirrhotic group. No significant difference was determined between gender distribution. A statistically significant difference was determined between HAI measurements of patients with CHB according to being cirrhotic (p=0.001). HAI measurements of cirrhotic patients were higher. There was a statistically significant difference between HAI, MCV, GGT, and AST measurements of patients with CHB according to being cirrhotic (p=0.020, p=0.038, p=0.028, p=0.017; respectively). HAI, MCV, GGT, and AST measurements and of the cirrhotic group were higher. A statistically significant difference was determined between albumin and PLT measurements of patients with CHB according to being cirrhotic (p=0.015, p=0.009; respectively). Albumin and PLT measurements of the cirrhotic group were less (**Table 2**, **Table 3**).

DISCUSSION

Liver biopsy can reveal many pathological diagnoses such as inflammation, necrosis, and lubrication. Nevertheless, the liver biopsy has innumerable limitations and this method is also associated with possible morbidity and mortality (25,26). In patients with CHB cirrhosis patients due to CHB, noninvasive tests that will provide information about the severity, activity of the disease, and fibrosis stage are required. Clinical studies are reporting that information can be obtained about the status and course of the disease by looking at MPV and NLR measurements with a simple CBC test (27,28). In our study, MPV values were determined to be significantly higher in patients with CHB compared to HCs cases (p=0.002). While it was not significant, it was observed that mean MPV values were higher in the cirrhotic group compared to the non-cirrhotic group (**Table 2**, **Table 3**, **Figure 1**). When we looked at MPV studies performed with patients with HBV and cirrhotic patients, MPV values were decited to be considerably higher also in inactive HBsAg carriers compared to HCs in a study performed in our country (15). Again, in a study performed with the number of patients similar to our study,

Table 1. Distribution of Descriptive Characteristics

Demographic characteristics (n=84)	
Age (year)	
Mean±SD	46,56±11.66
Min-Max (Median)	48 (24-73)
Gender; n (%)	
Female	30 (35.7)
Male	54 (64.3)
Groups; n (%)	
Chronic hepatitis	54 (64.3)
Control	30 (35.7)
Features of chronic hepatitis group (n=54)	
Drug; n (%)	
Tenofovir	48 (88.9)
Entecavir	5 (9.3)
Lamivudine	1 (1.9)
Fibrosis; n (%)	
F0	2 (3.7)
F1	8 (14.8)
F2	16 (29.6)
F3	11 (20.4)
F4	4 (7.4)
F5	9 (16.7)
F6	4 (7.4)
Fibrosis groups; n (%)	
Non-cirrhotic	41 (75.9)
Cirrhotic	13 (24.1)

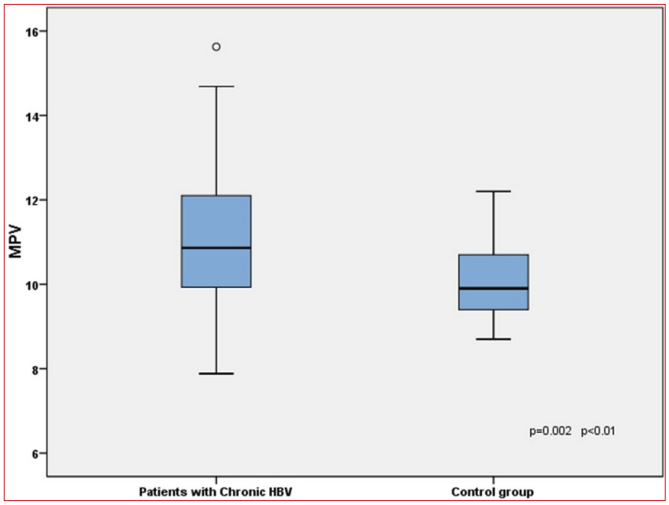

Figure 1. MPV distribution between Chronic Hepatitis group and the control group (MPV: mean platelet volume)

Table 2: Clinical characteristics of the study population

		Patients with Chronic HBV (n=54)	Control group (n=30)	p
Age (year)	Min-Max (Median)	24-73 (49)	31-65 (45.5)	[a]0.800
	Mean±SD	46.78±13.02	46.17±8.87	
Gender; n (%)	Female	19 (35.2)	11 (36.7)	[b]0.892
	Male	35 (64.8)	19 (63.3)	
ALT	Min-Max (Median)	10-316 (49.5)	6-51 (18)	[c]0.001**
	Mean±SD	72.35±67.90	21.43±11.10	
AST	Min-Max (Median)	14-312 (33,5)	12-31 (17)	[c]0.001**
	Mean±SD	47.50±47.07	17.87±4.64	
Neutrophil	Min-Max (Median)	1340-9220 (3290)	1870-7560 (3665)	[c]0.078
	Mean±SD	3617.78±1276.79	4051.67±1281.62	
Lymphocyte	Min-Max (Median)	920-4230 (2280)	1320-3940 (2195)	[a]0.582
	Mean±SD	2280.00±708.46	2367.00±656.70	
NLR	Min-Max (Median)	1.08-4.81 (1,69)	0.9-3.8 (1.7)	[c]0.351
	Mean±SD	1.98±0.81	1.81±0.69	
Hb	Min-Max (Median)	11.4-17.1 (15.1)	9.8-16.7 (14.5)	[a]0.194
	Mean±SD	14.68±1.39	14.23±1.73	
PLT	Min-Max (Median)	27.8-1180 (205)	172-390 (261)	[c]0.001**
	Mean±SD	222.13±146.54	257.73±46.13	
MPV	Min-Max (Median)	7.9-15,6 (10.8)	8.7-12.2 (9.9)	[a]0.002**
	Mean±SD	11.15±1.77	10.02±0.92	

aStudent t Test, bPearson's Chi-square Test, cMann Whitney U Test, **p<0.01

only MPV values were compared. In this aforementioned study, the patient sample was divided into two groups (group 1, F0-F2 fibrosis; group 2, F3-F4 fibrosis) and compared with the HCs group according to the METAVIR scores in liver biopsies of 59 patients with CHB and a significant relationship was determined between MPV measurement and advanced fibrosis in the CHB group (4). In another study performed with patients with HBV, MPV values were determined to be considerably higher in patients with CHB and severe CHB compared to HCs cases and patients with acute hepatitis (17). In another study, liver fibrosis grading was performed using transient elastography in 38 with patients CHB, NLR and MPV values were determined to be significantly higher in patients with CHB compared to HCs cases and it was reported that both NLR and MPV values could be predictive factors for increased hepatic fibrosis (8). In our study, while a statistically significant correlation could not be determined, NLR values were also elevated with increased liver fibrosis grades (**Table 2**, **Table 3**). The absence of a statistically significant p value may be related to the relatively low number of patients. Because as the degree of fibrosis increases in our study, NLR measurements also increase, as in similar studies in the literature. When we looked at studies in the literature performed with cirrhotic patients, it was reported that NLR value was a predictor of mortality independent of Child-Turcotte-Pugh (CTP), Model for End-Stage Liver Disease (MELD) scores and also could predict mortality in the subgroup of patients with low MELD scores in a study (21). In another study, NLR values were determined to be significantly higher in Acute-on-chronic liver failure patients compared to the HCs and it has been reported that it could be used as an independent predictor for 3-month mortality rate (19). In another study, 4 groups were constituted as HCs, CHB, decompensated cirrhosis due to CHB, and acute-on-chronic liver failure, and mean NLR values were determined to be 2.22, 2.54, 3.07, 3.41; respectively in these groups. A gradual correlation was detected between progressive disease and NLR (9). In another study, higher NLR was associated with worsening disease course and higher mortality in decompensated cirrhotic patients with CHB. Again, this aforementioned study reported that NLR values could be used as an independent predictor in the prediction of 30-day mortality similar to MELD score (18). In an interesting study performed in patients undergoing liver transplantation with a diagnosis of HCC occurred due to any reason, a significant correlation was determined between elevated NLR values and the risk for recurrence of HCC and recipient death (22).

Table 3: Clinical characteristics of patients with chronic hepatitis B

		Non-cirrhotic group (n=41)	Cirrhotic group (n=13)	p
Age (year)	Min-Max (Median)	24-73 (43)	30-73 (55)	d0.014*
	Mean±SD	44.29±12.23	54,62±12,76	
Gender; n (%)	Female	13 (31.7)	6 (46.2)	d0.506
	Male	28 (68.3)	7 (53.8)	
Drug; n (%)	Tenofovir	38 (92.7)	10 (76.9)	e0.147
	Entecavir	2 (4.9)	3 (23.1)	
	Lamivudine	1 (2.4)	0 (0)	
HAI	Min-Max (Median)	3-11 (6)	6-14 (8)	c0.001**
	Mean±SD	6.49±1.89	8.92±2.36	
ALT	Min-Max (Median)	10-291 (50)	23-316 (47)	c0.460
	Mean±SD	67.61±59.87	87.31±89.97	
Albumin	Min-Max (Median)	3.7-4.8 (4.3)	3.2-5 (4.2)	c0.015*
	Mean±SD	4.35±0.23	3.98±0.56	
AST	Min-Max (Median)	14-138 (27)	26-312 (48)	c0.020*
	Mean±SD	39.05±27.13	74.15±79.49	
ALP	Min-Max (Median)	10-119 (69)	56-192 (80)	c0.093
	Mean±SD	71.78±19.00	93.23±40.47	
GGT	Min-Max (Median)	11-118 (26)	9-216 (44)	c0.038*
	Mean±SD	33.76±23.98	76.46±69.32	
Total bilirubin	Min-Max (Median)	0.3-1.4 (0.8)	0.6-1.7 (0.8)	c0.824
	Mean±SD	0.82±0.26	0.89±0.35	
INR	Min-Max (Median)	0.9-1.4 (1)	1-1.4 (1.1)	c0.105
	Mean±SD	1.04±0.11	1.11±0.13	
WBC	Min-Max (Median)	4120-11000 (6450)	2520-13100 (6220)	c0.800
	Mean±SD	6593.17±1551.25	6895.38±2577.99	
Neutrophil	Min-Max (Median)	2110-6870 (3250)	1340-9220 (3640)	c0.331
	Mean±SD	3482.68±967.64	4043.85±1954.46	
Lymphocyte	Min-Max (Median)	1230-4230 (2200)	920-3030 (2290)	c0.530
	Mean±SD	2333.41±715.98	2111.54±683.76	
NLR	Min-Max (Median)	1.09-4.8 (1.7)	1.08-4.14 (2.24)	c0.134
	Mean±SD	1.86±0.68	2.36±1.04	
Hb	Min-Max (Median)	11.7-17.1 (15.1)	11.4-16.4 (14.1)	c0.261
	Mean±SD	14.82±1.33	14.23±1.54	
Htc	Min-Max (Median)	36.3-50.8 (44.8)	32.7-47.9 (43.1)	c0.331
	Mean±SD	43.92±3.66	42.33±4.68	
MCV	Min-Max (Median)	83.1-97.3 (89.1)	84-102 (93.7)	c0.028*
	Mean±SD	89.25±3.50	92.81±5.21	
PLT	Min-Max (Median)	27.8-1180 (216)	76-266 (166)	c0.009**
	Mean±SD	239.00±162.47	168.92±53.07	
MPV	Min-Max (Median)	7.88-15.63 (10.6)	9.12-13.75 (11.5)	c0.544
	Mean±SD	11.09±1.89	11.35±1.36	
AFP	Min-Max (Median)	1.3-13.1 (3.5)	2.4-36.7 (5.1)	c0.017*
	Mean±SD	4.14±2.35	8.68±9.09	

(cMann Whitney U Test, dFisher's Exact Test, eFisher Freeman Halton Exact Test **p<0.01, *p<0.05)

Limitations

Limitations of the current study are its retrospective design and the number of patients included is limited. However, comparison of two important laboratory markers with liver biopsy results is an advantage for the study. However, the comparison of two important laboratory markers with liver biopsy results of patients with chronic hepatitis B is an important privilege for the study. Future prospective, multicenter studies with a larger number of patients will provide more reliable results.

CONCLUSION

Similar to the literature also in our study, MPV values measured in patients with CHB were determined to be higher than the HCs group (**Table 1**, **Figure 1**). On the other hand, although there was no statistically significant difference, NLR measurements determined to be higher in the CHB patients than the HCs (**Table 1**). In this Study, in comparisons between cirrhotic and non-cirrhotic CHB patients, MPV and NLR measurements were observed to be mildly elevated in the cirrhotic group but a statistically significant difference did not occur (**Table 2**). This condition shows that MPV and NLR values also increase in patients with CHB directly proportional to the increase of liver fibrosis stage shown with biopsy and determined with the Ishak score. The number of patients and HCs investigated this study is similar to studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission Zeynep Kamil Women and Children Diseases Training and Research Hospital Ethics Committee (Date: 22.05.2019, Decision No: EY.FR.22-54).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Case Report

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The new onset seropositive rheumatoid arthritis after COVID-19 infection: coincidental or related

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an infectious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The relationship of COVID-19 with rheumatological disorders has been researched since 2019. Rheumatoid arthritis (RA) is one of the most common rheumatoid diseases. The relationship between RA and COVID-19 is particularly interesting due to common cytokines in etiopathogenesis. SARS-CoV-2 was involved in triggering RF-positive and ACPA-positive arthritis, which might be diagnosed as rheumatoid arthritis, but we cannot rule out the possibility that the onset of this arthritis could have been coincidental. We report the case who has the first flare of RA with a high titer of Rheumatoid Factor (RF) and Anti Citrullinated Protein Antibody (ACPA) after mild SARS-CoV- 2 infection.

Keywords: Rheumatoid arthritis, COVID-19, Cytokine pathways

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by joint inflammation, which affects approximately 1% of the population. Multiple genetic and environmental factors have been associated with an increased risk for RA. Of these, the strongest associations have been seen with female sex, a family history of RA. There is also renewed interest in mucosal inflammation and microbial factors as contributors to the development of RA (1). The relationship between RA and infectious diseases is very complex. Few studies have a possible link between breathing and lung-related viral infections and the development of RA (2). In a large Korean study, the authors watched that infections with endemic human coronavirus, parainfluenza virus, and metapneumovirus coincided with an increased rate of development of RA (3). It is still discussed that seropositive arthritis can be triggered by COVID-19 infection. (4) Herein we report a young male patient with the onset of seropositive RA after mild COVID-19 infection.

CASE REPORT

A 23-year-old male patient has been admitted to the Physical Medicine and Rehabilitation (PMR) outpatient clinic with complaints of widespread arthralgia, muscle pain, and fatigue for three days. No swollen, tender, or restricted joints were found in his examination. He had no neurological deficits. Sacroiliac compression tests were bilaterally negative. Schober test was measured 6 cm. Skin examination was normal. His body temperature was 36.5°C. He never had similar complaints before. He stated that there is no rheumatological disease in the family. There was no additional feature in his rheumatological questioning. He said he had no sore throat, runny nose, headache, or cough. He had no history of smoking. There was no history of suspicious contact with a COVID-19 case. Laboratory tests showed white blood cell (WBC) of 5.66×10^3/µL, platelet of 305×10^3/µL, Sedimentation rate of 41 mm/h, D-dimer of 0.6, and C-reactive protein (CRP) of 82 mg/dL. COVID-19 polymerase chain reaction (PCR) test performed on the patient's nasopharyngeal swab was positive (**Table 1**). COVID-19 involvement was not detected in lung tomography. The patient was quarantined at home. Favipiravir starting dose was 2×1600 mg on the first day, then four days maintenance dose was continued with 2×600 mg. Low molecular weight heparin Enoksaparin Sodium at a dose of 1×40 mg (Equivalent to 4000 anti-Xa IU) was started. Completing the 14-day quarantine period, the patient applied to the PMR outpatient clinic for control. He stated that his complaints of weakness and fatigue decreased, but joint pain continued, especially in the hand joints. On examination, bilateral 2nd and 3rd metacarpophalangeal joints and bilateral 2nd and 3rd proximal interphalangeal joints were swollen and sensitive to pressure. Periarticular osteoporosis, subchondral cysts, erosion, and narrowing of the bone marrow were not detected on hand radiography. CRP decreased to 57,37. Sedimentation was 41, D-dimer was persisting at 0.6; his hemogram was normal. RF 116,4 positive at high titer, anti-ccp> 200 positive at high titer. There was no cough or shortness of breath. Lung sounds were natural. Internal medicine was

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consulted in terms of additional infection and prolonged COVID-19 infection, no additional infection was detected, and prolonged COVID-19 was not considered. The patient was referred to the Rheumatology outpatient clinic. He was evaluated as early RA according to the American College of Rheumatology (ACR) 2010 criteria. Low dose corticosteroid and Leflunomide 10 mg 1×1 were started. The patient came for control one month later. This time CRP had decreased to 24. Sensitive and swollen joints were not detected. He was followed up in the outpatient clinic without any change in his treatment. Although the acute phase reactants continue to decrease, the RF titer remains high. Anti-CCP titer could not be followed by economic concerns.

Table 1. Laboratory findings of clinical course

	On Admission	When arthritis develops (day15)	One month after treatment (day 45)
WBC (×10³/µl, 3.5-10.5)	5.66	8.03	8.17
Neutrophil#(10³/µl, 1.7-73.95)	49.3	3.95	4.10
Neutrophil% (42-72)	29.9 L	49.3	50.2
Lymphocyte# (10³/µl, 0.9-2.9)	2.53	2.53	2.79
Lymphocyte % (23-50)	41.3	31.5	34.1
Hemoglobin (g/dl, 13.5-17.5)	13.5	13.5	15.4
Platelet (×10³/µl, 150-450)	305	306	302
Urea (mg/dL, 17-43)	20	18	19
Creatinine (mg/dL, 0.67-1.17)	0.78	0.66	0.76
Uric acid (mg/dL, 3.5-7.2)		6.3	
AST (IU/L, 0-50)	29	25	16
Sedimentation rate (mm/h, 2-15)	41 H		
CRP (mg/L, 0-5)	82,68 H	57,37 H	24,28 H
D-dimer (mg/L, 0-0.55)	0.6 H	0.6 H	
RF (IU/mL, 0-14)		112.1 H	116.4 H
Anti-CCP (U/mL, 0-5		>200	
COVID-19 PCR from nasopharyngeal swab	Positive		

Anti-CCP: Anti- Cyclic Citrullinated Peptide; AST: aspartate transaminase; CRP: C-reactive protein; PCR: polymerase chain reaction; RF: Rheumatoid Factor, WBC: white blood cell.

DISCUSSION

Novel coronavirus disease-2019 (COVID-19) has been a global pandemic since November 2019. It has a broad clinical spectrum from asymptomatic or mild forms to clinical conditions that may lead to multi-organ failures(5). Studies have shown that among COVID-19 patients, myalgia is the most common musculoskeletal symptom observed with a prevalence ranging from 30 to 36% (6,7). The number of COVID-19 positive patients presenting with pain, while without any initial respiratory tract symptoms were remarkable (8). Joob et all reported that arthralgia may be the first symptom of COVID-19 (9). Weakness and fatigue are also known to be frequently seen in COVID-19 infection (10). Our case presented with arthralgia, myalgia, and weakness without fever and lung findings. COVID-19 should be kept in mind for patients who apply to PMR outpatient clinics with these complaints and should be vigilant. In addition, distance and protective equipment rules should be followed not only in areas reserved for COVID-19 patients but also in other polyclinics.

Since the outset of the COVID-19 pandemic, numerous risk factors for the severe disease have been identified. The relationship between rheumatological diseases and COVID-19 is also one of the topics that are curious and continue to be investigated (11). A growing number of cases of COVID-19-related arthritis are being reported in the literature. Some of these are cases of reactive arthritis that develop after COVID-19 infection. That was negative for rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) (12,13). However, cases like our patient who developed seropositive rheumatoid arthritis after COVID-19 are really interesting. Roongta et al. describe a 56-year-old female patient who was treated as post-covid reactive arthritis but developed seropositive RA during follow-up. They also stated that they had six more patients diagnosed with seropositive RA after COVID-19. All these patients have previously documented negative serology (14). Perrot et al. reported a 60-year-old female who developed seropositive rheumatoid arthritis 25 days after COVID-19 infection with lung involvement. In this case, she was already detectable ACPA when the patient tested positive for SARS-CoV-2; however, by the time she developed arthritis, her ACPA titers had substantially increased. They thought that COVID-19 infection was a factor that would trigger the onset of RA in this patient who did not have joint pain before (15). Baimukhamedov et al. reported a 67 years-old male patient who developed arthritis with a high RF approximately one month after the resolution of COVID-19 symptoms and almost 5 months later progressive increase of ACPA. This patient also has no previous joint pain and COVID-19 has progressed with lung involvement. It is noteworthy that the patient's RF value before COVID-19 was negative (16). We did not measure autoantibody levels before the onset of symptomatic arthritis. However, we know that the patient did not have joint complaints before. Contrary to the seropositive cases that developed after COVID-19, our patient did not have lung involvement and the severity of COVID-19 disease is milder.

Triggering of autoimmunity by COVID-19 infection has been proposed. Autoimmune diseases like lupus, Kawasaki disease, systemic vasculitis, APLA syndrome have been reported post-COVID-19 (4). Vlachoyiannopoulos et all tested the sera of 29 unselected severely ill patients with COVID-19 with positive SARS-CoV-2 PCR and found that one patient was positive for anti-CCP Antibodies (17). Derksen et al have conducted serology studies on 61 patients, 5 weeks after COVID-19 infection, and found no increase in the incidence of anti-citrullinated cyclic peptide (anti-CCP) antibodies. Also, they found that the clinical and autoantibody characteristics of three patients from another cohort with seroconversion were similar to the regular patients with RA. However, pre-infection serological data are lacking. The main question raised is whether the development of post-COVID RA is coincidental or connected (18)? The relationship between RA and infectious diseases is very complex. Few studies have investigated a potential link between respiratory viral infections and the development of RA(2). In a large Korean study, the authors observed that infections with endemic human coronavirus, parainfluenza virus, and metapneumovirus coincided with an increased rate of development of RA(3). Thus, the COVID-19 pandemic maybe could potentially lead to an increase in cases of RA.

Cytokine pathways and their signaling can be the cause of the onset and pathogenesis of many diseases such as autoimmune diseases and COVID-19 infection (19). Rheumatoid arthritis is a chronic and systemic autoimmune response to multiple joints with unknown ethology. It is characterized by hyperplasic synovium, production of cytokines, chemokines, autoantibodies like rheumatoid factor (RF), and anticitrullinated protein antibody (ACPA). Cytokine-mediated pathways are central to the pathogenesis of RA. Among the proinflammatory cytokines, IL-1α/β and TNF-α trigger the intracellular molecular signaling

pathway responsible for the pathogenesis of RA that leads to the activation of a mesenchymal cell, recruitment of innate and adaptive immune system cells, activation of synoviocytes which in term activates various mediators including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-8 (IL-8), resulting in inflamed synovium, increase angiogenesis and decrease lymphangiogenesis (20). As the same cytokine such as IL-6 and TNF-α activation leads to over-activation of innate immunity in COVID-19 (2). The hierarchical order of cytokines involved in COVID-19 is not yet known, but mediators that are currently therapeutically targeted in RA and autoinflammatory syndromes seem to be of central importance (21). Many drugs (Corticosteroids, IL-6 receptor blockers, TNF inhibitors) that are commonly used in the treatment of RA have been proposed as possible therapies for COVID-19 as a consequence of the increased knowledge about the pathophysiology of the infection(2). The cytokines involved in COVID- 19 and RA are common. This may support the idea that the onset of seropositive RA can be induced with COVID-19. We know that inflammatory cytokines are released more in patients with severe COVID-19 clinic (22). Roongta et all claimed that moderate to severe lung involvement may be a risk factor for anti-CCP antibody generation and in that way RA (14). Derksen et all expressed severe (pulmonary) inflammation in COVID-19 could be a trigger for the break of tolerance to citrullinated proteins. Proinflammatory cytokine levels and neutrophil extracellular trap formation can indeed provide a source of citrullinated proteins in an inflammatory pulmonary environment (18). On the contrary to what is claimed, there was no lung involvement in our patient and the disease is mild. Derksen et all say that one could also argue that these potential triggering factors subside as the SARS-CoV-2 infection wanes. This could reduce the chance that they would still be involved in causing an ACPA response many months later (23). They argued that the seroprevalence of ACPA is not increased after COVID-19 and that most patients presenting with polyarthritis after COVID-19 look like regular RA patients. We asked ourselves if our patient had not been infected with SARS-CoV-2, would he still have developed RA? We can't know the answer to this question with our current knowledge. However, the development of RA in a young male patient with no family history and no previous joint complaints is a very rare condition. Perhaps genetic factors may be effective in these cases (19). We think that COVID-19 may trigger the development of RA in genetically predisposed individuals It is probably too early to figure out that this event is only by chance. Time will tell whether a reasonable connection between these two events exists, or whether it may be a coincidence, or whether it may be a coincidence It appears likely that more cases of seropositive RA after COVID-19 will be reported in the future. Research needs to focus on large cohorts rather than individual case studies. This would enable the researchers to find out the key aspects of the COVID-19 and RA relationship (24).

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Case Report

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A rare drug fever due to everolimus use in a patient with liver transplantation: a case report during the COVID-19 pandemic

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ABSTRACT

Drug-induced fever is an uncommon, difficult-to-diagnose complication which is one of the possible causes of fever of unknown origin. In addition, COVID-19 infection is also a cause of fever in these pandemic days we live. Everolimus (EVR), an inhibitor of the mammalian target of rapamycin (mTOR), is employed as an immunosuppressant in combination with calcineurin inhibitors, following a procedure of organ transplantation, and as a proliferation signal inhibitor coated on a drug-eluting stent and in cancer therapy. EVR has many adverse effects that require follow-up, but fever is not one of the well-known adverse effects thereof. In our literature search, we have found only a single case of fever due to EVR use which had been reported in a patient following a cardiac transplantation in 2004. On the other hand, our case is a patient with a diagnosis of alcohol-induced liver cirrhosis and hepatocellular carcinoma who has been subjected to a liver transplantation has developed fever in the course of our follow-up just after the initiation of EVR treatment at the third month post-transplantation and during the COVID-19 pandemic.

Keywords: Liver transplantation, everolimus, drug fever

INTRODUCTION

Drug-induced fever (DIF) is most often the consequence of a hypersensitivity reaction, and its features resemble those of an allergic response. As a mTOR derived immunosuppressant EVR acts to prevent acute allograft rejection which is still one of the hampering factors for long-term survival following an organ transplantation (1,2). Infections are the most common cause of fever in patients with organ transplants and immune suppression, but may be due to organ rejection or drugs. Adverse effects of EVR include hyperlipidemia, hypertension, myelosuppression, lymphoceles, interstitial pneumonitis, various infections, renal dysfunction, delayed wound healing, proteinuria, and oral ulcers. In case of the development of fever following liver transplantation (LT), the presence of an infection is the first thing considered to be the etiological cause thereof since drug fever due to EVR use is not well known (3,4). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/COVID-19) pandemic is a worldwide emergency (5,6). In addition, in the days we followed our case, the COVID-19 pandemic was ongoing and was considered as the cause of fever.

CASE

We herein report a case of a 68-year-old man who have undergone a LT due to alcohol-induced liver cirrhosis and hepatocellular carcinoma (HCC). In accordance with the Milan criteria, the said patient has been subjected to a LT from a living donor, and followed-up for the subsequent three months with post-operative immunosuppression treatments including methylprednisolone 20 mg/day, tacrolimus 3 mcg/day, and mycophenolate mofetil 1000 mg/day. Towards the end of the third month after transplantation, in the said patient, who had a history of HCC, the dose of tacrolimus was decreased and a treatment with EVR was initiated starting morning and evening. And a few days later, he was admitted to our polyclinic with complaints of sore throat, post-nasal drainage, dry cough, and fever up to 39°C requiring paracetamol use. No systemic finding was detected except oropharyngeal hyperemia, and coarse bilateral lung sounds. The patient was hospitalized in our service, and his vital findings were followed-up through COVID-19 polymerase chain reaction (PCR) test, routine blood, urine and stool tests, tacrolimus and EVR tests for detecting the respective blood levels, tests for blood CMV DNA level, brucella agglutination and antibody tests, PA chest radiography, thorax CT. In initial tests, C reactive protein (CRP) values, an indicator of inflammatory response, were very high up to 207.3 mg/L (reference range: 0-5 mg/L), COVID-19 PCR test negative, liver function tests were within normal limits, no rejection finding was present, and whole blood count, renal functions, lipid profiles, thyroid function tests, and blood tacrolimus and EVR levels were all within normal limits. On the day of

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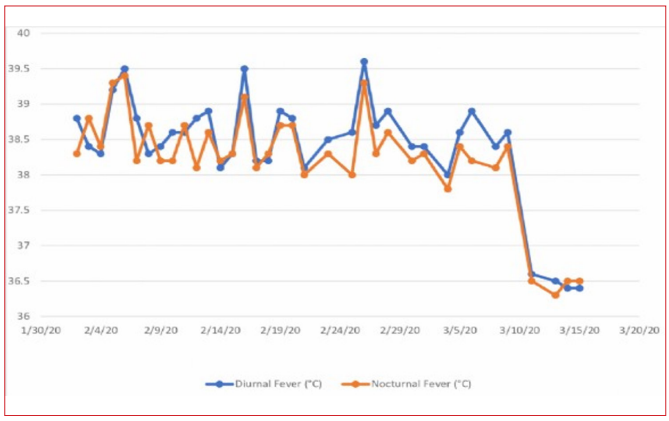
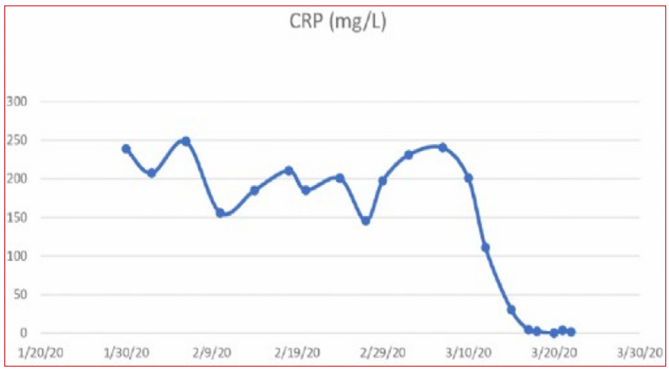
hospitalization, a fever of 38.3°C occurred, and thereupon, blood and urine cultures were taken, and a treatment with ceftriaxone was started. In the follow-up of patient, exacerbations of fever above 38°C, sometimes starting with chills and shivering, were observed twice each day (**Graphic 1**). The patient exhibiting a persistent fever and showing no growth in his cultures was closely monitored by the department of infectious diseases, treatment with ciprofloxacin was included in his cure on the third day of the ceftriaxone treatment as he was still having a fever, and due to the persistence of fever by day 7, both antibiotics were discontinued to start a treatment with ertapenem. Despite such efforts, the presence of fever peaking twice a day throughout the hospitalization period continued without any cease for six weeks (**Graphic 1**). Echocardiography, paranasal sinus CT, cranial MR, neck CT, thorax CT, and abdomen CT and PET-CT tests were normalized. In thorax CT, there was no suspicious appearance of COVID-19 (viral pneumonia) in thorax CT and the COVID-19 PCR test was negative. With the imaging and laboratory results shedding light on the possible presence of any lymphoproliferative and hematological disorders, but no finding indicating the presence of a hematological disorder was detected. Gastroscopy and colonoscopy were performed in which no relevant feature was found. Quantiferon tuberculosis test which had shown a negative result before transplantation was repeated, and a negative result was obtained again. Upon a re-consideration of his immunosuppressive cure, the treatment with EVR was discontinued, and the dose of tacrolimus was increased. After such discontinuation of the treatment with EVR, the frequency of fever has decreased with the absence of fever about 5 days later, and in parallel therewith, CRP levels which had increased considerably upon the initiation of the EVR treatment and continued to be very high until the said treatment was discontinued have also shown a in the **Graphic 2**.



Graphic 1. Results of daily (day and night) fever (°C) measurements of patient



Graphic 2. Daily blood CRP (mg/L) value monitoring (CRP: C-reactive protein)

DISCUSSION

According to our literature search, a report from 2004 is the only case of fever associated with EVR use in which the cause of a persistent fever in a patient undergoing a cardiac transplantation was reported as a DIF associated with EVR use (7). In the literature search, two cases (after renal transplantation and LT) of fever associated with the use of sirolimus which is another mTOR inhibitor were identified (8,9). All laboratory tests of our patient, except an increased CRP which is an inflammatory indicator. The agents that are most commonly associated with a DIF are penicillins, quinidine, phenytoin, NSAID, procainamide, antituberculars, methyldopa (10). Making a diagnosis may be particularly difficult if the presence of the infection required the use of a drug, such as vancomycin against a suspected bacteraemia, or isoniazid against tuberculosis (11). Symptoms of drug fever may include relative bradycardia, chills, and fatigue, as well as rash, but in some definitions of such symptoms any kinds of dermatologic symptoms are excluded. Laboratory tests may reveal the presence of eosinophilia, neutropenia, increased aminotransferases, thrombocytopenia, an increased erythrocyte sedimentation rate or CRP (12-14). However, an establishment of a diagnosis does not necessarily require the presence of such results. In our case, after we have failed to identify any infection (including COVID 19 infection), immune mediated disorder, or malignancy, a causative relationship was considered. In addition, the resolution of symptoms within the clinical course, and the normalization of inflammatory markers (CRP) following the discontinuation of the treatment with EVR have also supported this notion.

CONCLUSION

Fever is not a well-known side effect of EVR therapy. There were no reports in the literature except for fever due to EVR in a patient after heart transplantation in 2004. In this case report, a long-term fever of unknown origin etiological study was conducted to prove that fever is an DIF related to EVR. With this case, it is aimed to draw attention to possible drug fevers that may develop after successful organ transplants, which have increased proudly in our country and in the world. Thus, the labor, time and economic losses spent for similar cases can be avoided.

ETHICAL DECLARATIONS

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Note: Summary of this study; Presented as a poster presentation PP-239 at the 38th National gastroenterology congress held in Antalya on 16-21 November 2021 (a rare case of drug fever due to the use of everolimus in a liver transplant patient during the COVID-19 pandemic. 38th National Gastroenterology Week 16-21 November 2021 Antalya PP-239 P:723.).

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