e-ISSN: 2791-9250

DAHUDER MEDICAL JOURNAL

Volume 3 · Issue 1 · January 2023

DAHUDER MEDICAL JOURNAL

Available at http://dergipark.org.tr/en/pub/dahudermj

INTERNATIONAL EDITORIAL BOARD MEMBERS

Table of Contents

Letter to the Editor

Family Medicine

DOI: 10.56016/dahudermj.1194231

DAHUDER Medical Journal

e-ISSN: 2791-9250

Right time for the community based mental health care

Genco Görgü[1], Ozden Gökdemir[2]

[1]*Department Family Medicine, Marmara District State Hospital*

[2]*Department of Family Medicine, Izmir University of Economics, Faculty of Medicine, İzmir, Turkey*

Dear Editor,

The World Health Organization has produced a series of publications to create the general framework of mental health services. One of the main data sources is the WHO guide on community mental health services and the document promoting person-centered and human rights-based approaches. It includes the regulation of service providers' relations with the housing, education and employment sectors at the point of implementation of regional and national policies and the promotion of actions that are respectful of human rights and focused on recovery. It is a guide that offers various technical packages for the establishment and successful implementation of community-oriented mental health services. Various international framework agreements, including the United Nations Convention on the Rights of Persons with Disabilities also suggest the establishment of community-oriented mental health services. The common goal of up-to-date medical evidence-based information and international policymakers is to make the community-based mental health service model permanent on a global scale, especially in low-income and developing countries. [1]

The USA experience observed in the social crisis environment created by the Coronovirus epidemic has revealed the social dimension of mental health services. Fragile and oppressed masses of people have also been the losers of the pandemic period. The marginalization of people with mental health problems is a situation we frequently encounter in both public policies and daily life practice, and causes them to form a disadvantaged group beyond other illness experiences. (stigma, sanism). The high poverty rate associated with mental problems, housing and employment discriminations that cannot be explained by only financial contradictions have deepened the already existing problem. Individuals whose diseases were in remission or who were healthy before the epidemic also faced individual and social trauma due to the losses and economic problems they experienced. A healthcare service that is fast, accessible and capable of assessing sociocultural norms is perhaps more urgent than ever. Moreover, before the global epidemic, even in developed countries, the health service provided by a central organization was not sufficient. Aside from the ignoring of individuals with differences such as race, gender, sexual orientation by the central health authority; A mental health service that is not community-oriented and does not come into contact with primary health care services is also inadequate in terms of accessibility, clinical effectiveness and cost-effectiveness. [2]

Addiction is a scourge that humanity is fighting on a global level, just like infectious disease epidemics. Although this struggle is fought in a different and unique psychosocial environment in every geography, it is the common problem of all nations. With this understanding, it has found a place in the United Nations Sustainable Development Goals Agenda. In addition to traditional preventive and therapeutic

Received: *October 25, 2022;* ***Accepted:*** *January 5, 2023;* ***Published Online:*** *Januaray 29, 2023*

How to cite this article: *Görgü G, Gökdemir Ö, Right time for the community based mental health care. DAHUDER MJ 2023,3(1):1-3. DOI:10.56016/dahudermj.1194231*

Address for correspondence: *Ozden GOKDEMİR, Associate Professor, Department of Family Medicine, İzmir University of Economics, Faculty of Medicine, İzmir, Turkey. E-mail: gokdemirozden@gmail.com*

interventions, in-service training of health personnel and health literacy and education of patients are also important. In this respect, it is important that the patient and the physician have access to each other. Large psychiatric centers may be mandatory for some clinical situations, but are not suitable for a long-term relationship that will provide treatment and education simultaneously. In the fight against addiction, interventions from a biological, psychological and social perspective that take the individual with all dimensions of his/her existence are necessary. On-site, face-to-face psychosocial intervention will strengthen the hand of health care providers. In this model, the evaluation and protection of the patient's social functionality is also more easily handled as a measure of recovery. 3

One of the greatest achievements of community-based mental health services is the autonomy of the individual. Maintaining patient autonomy is at the center of almost all the elements of contemporary patient-physician relationship adopted in both mental health and other clinical practices of medicine, such as shared decision making and establishing common ground. Patient autonomy is the basic condition of effectiveness and sustainability in all primary health and mental health services such as self-care, medication and treatment compliance, consent, participation in individual and group therapies, family and marriage counseling services, and home care services, and can be strengthened with a community-oriented perspective. [4]

A multicenter study, centered in Southeast Europe, evaluated the outcomes of community-based mental health service delivery in regions where there are already central mental health institutions. In order to improve service quality, service provider units have been established. These units are named as multidisciplinary community mental health teams. Team members include a psychiatrist, psychologist, social worker, and one person identified as a peer worker. This participant is a patient with previous mental illness experience. Adaptations can be made in the structure of these core units due to regional and case-based reasons. The number of nurses or social workers in the team can be increased within the framework of needs and opportunities. Family physician and other primary care workers can be added to the team. The aim of this multidisciplinary team is to ensure that the mental health service offered is compatible with the conditions of the individual, in other words, to tailor the treatment. In this context, besides the guiding attitude of the team coordinator, it is also important to ensure the feedback process and mutual participation. It is important that the community-based mental health initiative is measurable, transferable and sustainable, both in terms of providing effective service and having the quality of evaluation and data. [5]

Physical restrictions imposed to limit the spread of the virus during the global COVID-19 pandemic have forced healthcare providers to turn to digital alternatives. This has opened up new important opportunities in the midst of a real crisis. The digital infrastructure of the patient-centered approach has been provided with the accessibility of digital environments that allow the establishment of an instant synchronized relationship between the doctor and the patient located in different places. In addition, progress has been made in decision support systems and joint decision-making initiatives in solving complex clinical problems. The importance of social assistance and the support of one's environment in daily life emphasized the importance of a community-oriented perspective. [6]

Structural transformation in mental and physical health will strengthen the individual's self-will and autonomy. Community-based health care will be the mental health model of the twenty-first century that focuses on the individual who maintains well-being and functionality.

CONCLUSIONS

Authors' Contribution

Study Conception: ÖG,; Study Design: GG,; Supervision: ÖG,; Materials: GG, ÖG,; Data Collection and/or Processing: GG,; Statistical Analysis and/or Data Interpretation: ÖG,; Literature Review: GG, ÖG,; Manuscript Preparation: GG, ÖG and Critical Review: ÖG.

REFERENCES

1. Guidance on community mental health services: Promoting person-centred and rights-based approaches. Available at: www.who.int/publications/i/item/9789240025707. Accessed June 9, 2021.
2. Mental Health Care Was Severely Inequitable, Then Came the Coronavirus Crisis, Azza Altiraifi, Nicole Rapfogel. Available at: www.americanprogress.org/article/mental-health-care-severely-inequitable-came-coronavirus-crisis/ Accessed September 10, 2020.

3. Heijdra Suasnabar JM, Hipple Walters B. Community-based psychosocial substance use disorder interventions in low-and-middle-income countries: a narrative literature review. Int J Ment Health Syst. 2020 Oct 8;14:74. doi: 10.1186/s13033-020-00405-3.
4. Faria Damásio Dutra, Virginia, Rigone Bossato, Hércules, Pontes de Oliveira, Rosane Mara Mediating autonomy: an essential care practice in mental health. Escola Anna Nery Revista de Enfermagem [en linea]. 2017, 21(3), 1-8[fecha de Consulta 5 de Octubre de 2022]. doi: 10.1590/2177-9465-ean-2016-0284
5. Shields-Zeeman L, Petrea I, Smit F, Walters BH, Dedovic J, Kuzman MR, Nakov V, Nica R, Novotni A, Roth C, Tomcuk A, Wijnen BFM, Wensing M. Towards community-based and recovery-oriented care for severe mental disorders in Southern and Eastern Europe: aims and design of a multi-country implementation and evaluation study (RECOVER-E). Int J Ment Health Syst. 2020 Apr 22;14:30. doi: 10.1186/s13033-020-00361-y.
6. Kopelovich SL, Monroe-DeVita M, Buck BE, Brenner C, Moser L, Jarskog LF, Harker S, Chwastiak LA. Community Mental Health Care Delivery During the COVID-19 Pandemic: Practical Strategies for Improving Care for People with Serious Mental Illness. Community Ment Health J. 2021 Apr;57(3):405-415. doi: 10.1007/s10597-020-00662-z.

Review
İnternal Medicine
DOI: 110.56016/dahudermj.1195167

DAHUDER
Medical Journal
e-ISSN: 2791-9250

Approach to diagnosis and treatment of familial hyperlipidemia

Kübra Çerçi, İmge Bortay Tekin, Seyit Uyar

Department of Internal Medicine, Antalya Training and Research Hospital, Antalya, Turkey

ABSTRACT

Familial hyperlipidemia (FH) is an autosomal dominant inherited disease characterized by genetic disorders with severe high blood cholesterol levels. There are two forms of the disease which are homozygous and heterozygous FH. FH cases are generally caused by hereditorial mutations in the LDL receptor (LDL-R) gene and less commonly in genes encoding apolipoprotein B (Apo B) and pro-protein convertase subtilisin/kexin 9 (PCSK9) proteins. The risk of early-onset coronary artery disease (CAD) in FH patients is 20 times higher than the normal population. Early diagnosis and treatment of FH will greatly reduce the morbidity and mortality associated with CAD.

Keywords: Familial hyperlipidemia, heterozygous familial hyperlipidemia, homozygous familial hyperlipidemia, low-density lipoprotein receptor mutation

Familial hyperlipidemia (FH) is a common genetic disorder that causes early cardiovascular diseases and is responsible for approximately 20% of coronary artery diseases (CAD) especially seen under 45 years of age. However, the diagnosis of FH is often overlooked and patients are diagnosed after experiencing a major coronary event. Cardiovascular diseases could be significantly reduced by early diagnosis and treatment of these patients and their family members.[1]

FH is an autosomal dominant disease that is seen as a result of mutations in one or more genes that cause a significant increase in low-density lipoprotein (LDL) levels.[2] There are many mutations, but they are most common in 3 genes; 85-90% in the low-density lipoprotein receptor (LDLR) gene, 2-4% in the proprotein convertase subtilisin/kexin 9 (PCSK9) gene, and 1-12% in the apolipoprotein B (ApoB) gene.[3-5] Those who have more than one of the mutations are affected more than those who carry a single gene mutation. Homozygous individuals have very high total cholesterol levels (above 500 mg/dL) and often develop atherosclerotic cardiovascular disease before the age of 20 and death occurs before the age of 30 years.[6] The prevalence of the disease is reported at very different rates between societies, depending on ethnic differences and the diagnostic method. The prevalence is around 1 in 300 in heterozygous individuals and 1 in 300,000-400,000 in homozygous individuals.[4]

According to lipoprotein electrophoresis FH's are divided into 5 types; Type 2 FH is the most common type among these and with early diagnosis and treatment, the risk of cardiovascular disease can be significantly reduced in these people.[7, 8] Type 2 FH can be seen in homozygous and heterozygote forms. Homozygous individuals show the signs of the disease more seriously and at an earlier age than heterozygotes.

Received: *October 28, 2022;* ***Accepted:*** *December 27, 202;* ***Published Online:*** .....

How to cite this article: *Çerçi K, Bortay Tekin İ, Uyar S. Approach To Diagnosis And Treatment Of Familial Hyperlipidemia. DAHUDER M J 2023, 3(1):4-8. DOI: 10.56016/dahudermj.1195167*

Address for correspondence: *Seyit UAYR, M.D., Department of Internal Medicine, Akdeniz University School of Medicine, Varlık Mah., Kazım Karabekir Cd., 07100 Muratpaşa, Antalya, Turkey. E-mail: seyituyar79@hotmail.com.*

Clinic

Individuals with homozygous FH have severe, early atherosclerotic cardiovascular disease and generally die before the age of 30 years. However, heterozygous individuals also have high LDL cholesterol levels but the signs of atherosclerotic cardiovascular disease are noticed in middle ages. Apart from cardiovascular diseases, hyperlipidemia may also cause xanthomas and xanthelasmas on the skin, arcus cornea, xanthelasmas on the eyelids, lipemia retinalis, fatty liver disease and acute pancreatitis. [9-11] Individuals with FH often have a family history of hyperlipidemia.

If a person whose LDL cholesterol level is above 190 mg/dL has a family history of hyperlipidemia and/or early cardiovascular disease, or has xanthoma in himself or a family member, or has a family history of cardiac sudden death it is necessary to search FH and make further estimation. [1]

Evaluation of FH patients

The person should be assessed primarily for atherosclerotic cardiovascular diseases and risk factors. Those with early CAD, high cholesterol and tendon xanthoma that may be associated with FH in their family should be queried. Patients should be evaluated for the findings of cholesterol storage in the skin and eye and the presence of stenosis in peripheral arteries on physical examination. LDL and total cholesterol levels are high in the lipid profile of the patients, and high-density cholesterol (HDL) levels are normal or low. Triglyceride levels are mostly normal, and high levels do not rule out the diagnosis of FH. If possible, all patients with FH should be measured for lipoprotein (a) levels, because those with high lipoprotein (a) levels have higher risk of having cardiovascular diseases.

There is no clear consensus on when genetic testing should be used in the diagnosis and the treatment of hyperlipidemia. If a patient has been diagnosed with

Table 1. Dutch lipid clinic network diagnostic criteria for FH

Criteria	Points
1) Family history	
First-degree relative with known premature (men: < 55 years; women: < 60 years) coronary or vascular disease	1
First-degree relative with known LDL-C above the 95th percentile	
First-degree relative with tendinous xanthomata and/or arcus cornealis	2
Children < 18 years of age with LDL-C above the 95th percentile	
2) Clinical history	
Patient with premature (men: < 55 years; women: < 60 years) coronary artery disease	2
Patient with premature (men: < 55 years; women: < 60 years) cerebral or peripheral vascular disease	1
3) Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
4) LDL cholesterol levels	
≥ 325 mg/dl	8
251-325 mg/dL	5
191-250 mg/dL	3
155-190 mg/dL	
5) Genetic analysis	
Functional mutation in the LDLR, apoB, or PCSK9 gene	8
Diagnosis is based on the total number of points obtained	
A "definite" FH diagnosis requires > 8 points	
A "probable" FH diagnosis requires 6 to 8 points	
A "possible" FH diagnosis requires 3 to 5 points	

FH: familial hypercholesterolemia

FH, screening of all first-degree relatives, including children above the age of two, is recommended in some guidelines. In some different guidelines recommend that genetic tests could be done if the result of test will change the clinical decision.[12-14] Mutations of LDLR, ApoB and PCSK9 genes could be screened in clinical suspicion of homozygous FH, but their normality does not mean that there are no genetic defects because there may be other rare genetic disorders. There is no clear recommendation for genetic testing in individuals with heterozygous.

Diagnosis

For the diagnosis of FH, the presence of a genetic mutation (in one of the LDLR, ApoB or PCSK9 genes) or clinical characteristic symptoms together with a high LDL cholesterol level is required. If genetic tests are not performed, some diagnostic criteria can also be used for the diagnosis of FH; Dutch Lipid Clinic Network diagnostic criteria is the one of them (Table 1).[4, 15]

Heterozygous FH can be diagnosed by genetic tests or clinical criteria. In homozygous FH patients clinical diagnosis could be made with high LDL cholesterol levels (if untreated LDL cholesterol level is above 500 mg/dL or treated LDL cholesterol level is above 300 mg/dL) or with the presence of skin or tendon xanthoma before 10 years of age, or with family history that both parents have high LDL cholesterol levels. However, LDL cholesterol levels are only a determinant in the diagnosis of FH and LDL cholesterol values below 500 mg/dL without treatment, especially in young people, do not exclude the possibility of homozygous FH.

Differential diagnosis

Hyperlipidemia, skin xanthoma and early atherosclerotic cardiovascular diseases can also be seen together with rare genetic disorders such as familial combined hyperlipidemia, familial dysbetalipoproteinemia, hyperbetalipoproteinemia, cerebrotendinous xanthomatosis, juvenile xanthogranuloma and sitosterolemia.

Treatment

The objective of FH treatment is important to reduce LDL cholesterol levels and prevent cardiovascular diseases. Lifestyle changes including diet, physical activity and weight control should be suggested to reduce LDL cholesterol levels in all patients and cardiovascular risk factors should be corrected. Although the consensus about the treatment goals and where the end line is still not clear, the first step is to reduce LDL cholesterol level by 50%. Aspirin also should be added to the treatment because almost all patients with FH are at risk for atherosclerotic cardiovascular diseases.

Statins, ezetimibe, PCSK9 inhibitors, lipid apheresis and evinacumab could be used in the medical treatment of homozygous FH. Statins are the first medical agents because of their potent in LDL cholesterol lowering efficacy and high doses should be preferred. Ezetimibe can be added to the treatment in patients who do not reach the target LDL value with high-dose statin therapy. PCSK9 inhibitors (alirocumab and evolocumab) can be added to the treatment if there is no sufficient response in patients using statins and ezetimibe. PCSK9 inhibitors can decrease LDL cholesterol levels by 30% in individuals with homozygous FH. [16] If the LDL cholesterol level is still not reduced with these treatments lipid apheresis could be used as additional treatment option. Though lipid apheresis treatment is individualized according to the patient, generally it is applied in every 2 weeks on average. With this method, a 60-70% reduction could be achieved in LDL cholesterol levels. There are many different effective apheresis techniques that can separate lipids from plasma or whole blood. American Society for Apheresis (ASFA) reports lipid treatment as a category I indication for homozygous FH and as a category II indication for heterozygous FH patients. 16 Angiopoietin-like protein 3 (ANGPTL3) is a hormone produced in the liver that inhibits lipoprotein lipase. Evinacumab, a monoclonal antibody developed against ANGPTL3 has been recently used in the treatment of homozygous FH.[17]

In heterozygous FH, treatment is also started with high-dose statins. If there is no decrease above 60% in the LDL cholesterol level measured after 6-12 weeks, 10 mg/day ezetimibe is added to the treatment. If there is no additional 20-30% decrease in the LDL cholesterol level re-examined after 6-12 weeks in the combination of high-dose statin and ezetimib, a PCSK9 inhibitor is added to the treatment. Patients whose target LDL cholesterol level is still not reached with these treatments should be switched to third-line treatments, as mentioned above for homozygous FH patients.[18]

Goal of therapy

Reducing LDL cholesterol levels in patients with FH is the main goal of treatment, but this is not

always possible. Therefore, the target value could be changed for different patients according to the cardiovascular disease risk factors in patients. The target LDL cholesterol level should be 55 mg/dL in very high-risk patients with diabetes, atherosclerosis, stage 3-4 chronic kidney disease or a previous case of CAD. A target of 100 mg/dL may also be acceptable for individuals with low risk factors.

Treatment during pregnancy

Women of childbearing age are advised to avoid pregnancy while on statin therapy. If pregnancy is planned, statin should be discontinued 3 months in advance and should not be used again until the breastfeeding period is over. Since there is no proper treatment during pregnancy, cholesterol measurement is not recommended. Lipid apheresis is the safest therapy that can be used during pregnancy.[19]

Prognosis

Prior to statin therapy, patients with FH had a very high risk of early CAD and mortality rates. With new treatment methods, there have been significant improvements in the prognosis of the patients. Nevertheless, individuals with FH are at 3 times risk of fatal and non-fatal myocardial infarction than people with similar characteristics without FH.[20]

CONCLUSIONS

Authors' Contribution

Study Conception: SU, KÇ, İBT,; Study Design: SU, KÇ, İBT,; Supervision: SU, KÇ, İBT,; Literature Review: KÇ, İBT,; Manuscript Preparation: KÇ, İBT and Critical Review: KÇ, İBT.

REFERENCES

1. Goldberg AC, Hopkins PN, Toth PP, Ballantyne CM, Rader DJ, Robinson JG, et al. Familial hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol 2011; 5:S1. https://doi.org/10.1016/j.jacl.2011.04.003.
2. Gidding SS, Champagne MA, de Ferranti SD, Defesche J, Ito MK, Knowles JW, et al. American Heart Association Atherosclerosis, Hypertension, and Obesity in Young Committee of Council on Cardiovascular Disease in Young, Council on Cardiovascular and Stroke Nursing, Council on Functional Genomics and Translational Biology, and Council on Lifestyle and Cardiometabolic Health. The Agenda for Familial Hypercholesterolemia: A Scientific Statement From the American Heart AssociationCirculation.2015Dec 1;132(22):2167-92.https://doi.org/10.1161/CIR.0000000000000297.
3. Futema M, Whittall RA, Kiley A, Steel LK, Cooper JA, Badmus E, et al. Simon Broome Register Group, Humphries SE. Analysis of the frequency and spectrum of mutations recognised to cause familial hypercholesterolaemia in routine clinical practice in a UK specialist hospital lipid clinic. Atherosclerosis. 2013; Jul;229(1):161-8. https://doi.org/10.1016/j.atherosclerosis.2013.04.011.
4. Austin MA, Hutter CM, Zimmern RL, Humphries SE. Genetic causes of monogenic heterozygous familial hypercholesterolemia: a HuGE prevalence review. American journal of epidemiology. 2004;160:407-420. https://doi.org/10.1093/aje/kwh236.
5. Pirillo A, Garlaschelli K, Arca M, Averna M, Bertolini S, Calandra S, et al. LIPIGEN Group. Spectrum of mutations in Italian patients with familial hypercholesterolemia: New results from the LIPIGEN study. Atheroscler Suppl. 2017 Oct;29:17-24.https://doi.org/10.1016/j.atherosclerosissup.2017.07.002.
6. Humphries SE, Whittall RA, Hubbart CS, Maplebeck S, Cooper JA, Soutar AK, et al. Genetic causes of familial hypercholesterolaemia in patients in the UK: relation to plasma lipid levels and coronary heart disease risk. J Med Genet 2006; 43:943. https://doi.org/10.1136/jmg.2006.038356.
7. Bouhairie, Victoria Enchia,Anne Carol Goldberg. Familial hypercholesterolemia. Cardiology clinics vol. 33,2 (2015): 169-79. https://doi.org/10.1016/j.ccl.2015.01.001.
8. Oosterveer DM, Versmissen J, Yazdanpanah M, Hamza TH, Sijbrands EJ. Differences in characteristics and risk of cardiovascular disease in familial hypercholesterolemia patients with and without tendon xanthomas: a systematic review and meta-analysis.Atherosclerosis 2009;207:311-7. https://doi.org/10.1016/j.atherosclerosis.2009.04.009.
9. Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. Nat Rev Dis Primers. 2017 Dec 7; 3:17093. https://doi:10.1038/nrdp.2017.93. PMID: 29219151.
10. Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HA, et al. Cost effectiveness analysis of different approaches of screening for familial hypercholesterolaemia. BMJ 2002;324:1303. https://doi.org/10.1136/bmj.324.7349.1303.
11. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J 2013; 34:3478. https://doi.org/10.1093/eurheartj/eht273.
12. Graham CA, McIlhatton BP, Kirk CW, Beattie ED, Lyttle K, Hart P, et al. Genetic screening protocol for familial hypercholesterolemia which includes splicing defects gives an improved mutation detectionrate. Atherosclerosis2005; 182:331–40. https://doi.org/10.1016/j.atherosclerosis.2005.02.016.
13. Taylor A, Wang D, Patel K, Whittall R, Wood G, Farrer

M, et al . Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade project. Clin Genet 2010;77:572-80. https://doi.org/10.1111/j.1399-0004.2009.01356.x.

14. Haase A, Goldberg AC. Identification of people with heterozygous familial hypercholesterolemia. Current opinion in lipidology. 2012;23:282-289.https://doi.org/10.1097/MOL.0b013e3283556c33.
15. Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014; 35:2146.https://doi.org/10.1093/eurheartj/ehu274.
16. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. J Clin Apher.2019;34:171–354. https://doi.org/10.1002/jca.21705. Referans17 Tikka A, Jauhiainen M. The role of ANGPTL3 in controlling lipoprotein metabolism. Endocrine ,2016; 52:187–193. https://doi.org/10.1007/s12020-015-0838-9.
17. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, V, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008; 358:1431. https://doi.org/10.1056/NEJMoa0800742.
18. Thorogood M, Seed M, De Mott K. Guideline Development Group. Management of fertility in women with familial hypercholesterolaemia: summary of NICE guidance. BJOG 2009 Mar;116(4):478-9. https://doi: 10.1111/j.1471-0528.2008.02084.x.
19. Nanchen D, Gencer B, Muller O, Auer R, Aghlmandi S, Heg D, et al. Prognosis of Patients With Familial Hypercholesterolemia After Acute Coronary Syndromes. Circulation 2016; 134:698. https://doi.org/0.1161/CIRCULATIONAHA.116.023007.

Original Article
Internal Medicine
DOI: 10.56016/dahudermj.1193872

DAHUDER Medical Journal
e-ISSN: 2791-9250

The relationship between monocyte/HDL cholesterol ratio and chronic kidney disease stages, single center study

İhsan Solmaz[1], Ömer Faruk Alakuş[1], Yusuf Yakut[1], Yunus Tekin[1], Sedrettin Koyun[1], Eşref Araç[2]

[1]Department of Internal Medicine, University of Health Sciences, Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey
[2]Department of İnternal Medicine, University of Dicle Training and Research Hospital, Diyarbakır, Turkey

ABSTRACT

Objectives: Chronic kidney disease (CKD) is an increasing public health problem. It is very important to know the definition of CKD, its risk factors and to predict the progression of its stages. Recently, the monocyte/HDL ratio (MHR) has been thought to be a new marker of inflammation and oxidative stress. In this study, it was aimed to investigate the relationship between stages and MHR in patients with stage 3A, stage 3B and stage 4 CKD.

Methods: A total of 632 patients with CKD, aged 18 years and older, with stage 3A, stage 3B and stage 4 (eGFR) according to CKD stage were included in our study. Our study is retrospective and the data of the patients were obtained from the hospital system. Kruskal-Wallis and post hoc Tukey HSD tests were used for statistics. $p < 0.05$ was considered statistically significant.

Results: The mean age of the patients included in the study was 63.4 ± 14.91(min:18max:98) and 305 (48.25%) of these patients were male and 327 (51.75%) were female. According to eGFR, 155 (24.5%) of the patients were stage 3A, 150 (23.8%) were stage 3B, and 327 (51.7%) were stage 4. In the statistical study of the groups divided into CKD stages with MHR, there was no significant difference between the groups (*p*: 0.245), while there was statistical significance for gender and hypertension (*p*: 0.004 and p: 0.044, respectively).

Conclusion: As a result of this study, we concluded that MHR is not affected by CKD stages.

Keywords: Monocyte-to-HDL ratio; Chronic kidney disease; Stage

Chronic kidney disease (CKD) is an important public health problem with an increasing incidence in our country and in the world. It is predicted that the number of patients to be treated with dialysis will double in the next 10 years. Regardless of the initial cause, the most important problems in chronic kidney disease are progression to end-stage renal disease (ESRD), complications due to loss of kidney function and increased cardiovascular risk due to CKD. The severity of these problems increases with the progression of kidney disease, and the chances of adequate treatment of these problems decrease. Therefore, it is very important to prevent the development of CKD and/or to catch it in the early stages and to stop the progression to ESRD. Concordantly, it is very important to know the definition of CKD and the risk factors for CKD, as well as to predict the progression of CKD stages.[1]

High-density lipoprotein HDL cholesterol (HDL-C) protects endothelial tissue from the destructive effects

Received: *October 25, 2022;* ***Accepted:*** *January 02, 2023;* ***Published Online:*** *January 29, 2023*

How to cite this article: *Solmaz İ, Alakuş ÖF, Yakut Y, Tekin Y, Koyun S, Araç E. The relationship between monocyte/HDL cholesterol ratio and chronic kidney disease stages, single center study. DAHUDER M J 2023;3(1):9-12. DOI: 10.56016/dahudermj.1193872*

Address for correspondence: *İhsan SOLMAZ, MD. Department of Internal Medicine, University of Health Sciences, Gazi Yasargil Training and Research Hospital, Diyarbakır, Turkey. E-mail: hsan2157@gmail.com*

Table 1.

	STAGE 3A	STAGE 3B	STAGE 4	TOTAL	*p*
Number of patients	155(24,5%)	150(23,8%)	327(51,7%)	632(100%)	
Age	59,2 ± 14,2	65,3 ± 12,7	64,5 ± 15,8	63,44	0,000
Gender					0,004
Male	91(29,83%)	75(24,59%)	139(45,57%)	305(48,25%)	
Female	64(19,57%)	75(22,93%)	188(57,49%)	327(51,75%)	
DM	67(21,96%)	71(23,27%)	167(54,75%)	305(48,25%)	0,265
HT	138(23,54%)	137(23,37%)	311(53,07%)	586(92,72%)	0,044
CAD	99(23,07%)	112(26,1%)	218(50,81%)	429(67,87%)	0,104

DM: Diyabetes mellitus, HT: Hypertension, CAD: Coronary Arter Disease

of low-density lipoprotein cholesterol (LDL-C) and also inhibits the oxidation of LDL-C. HDL-C also has antithrombotic, anti-inflammatory and antioxidant effects.[2] Monocytes and macrophages are cells that play an important role in the synthesis and release of proinflammatory and pro-oxidant cytokines. Recently, it has been thought that the monocyte/HDL ratio (MHR) may be a new marker of inflammation and oxidative stress due to the proinflammatory effect of monocytes and the anti-inflammatory and antioxidant effects of HDL cholesterol.[3]

Along with the anti-inflammatory and antioxidant effects of HDL-C, and the pro-inflammatory effect of monocytes, MHR reflects inflammation and oxidative stress. This ratio has been used in many studies to determine whether inflammation and atherosclerosis contribute to the etiopathogenesis of cardiovascular and cerebrovascular diseases.[4-8]

In this study, it was aimed to investigate the relationship between stages and MHR in patients with stage 3A, stage 3B and stage 4 chronic kidney disease.

METHODS

Patients diagnosed and followed up with stage 3A, stage 3B and stage 4 chronic kidney disease in Diyarbakir Gazi Yaşargil Training and Research Hospital Internal Medicine or Nephrology polyclinics were included in this study. Patients' data such as age, gender, biochemical parameters, hemogram, lipid profile, crp, comorbidity were recorded retrospectively through the hospital data processing system. With the eGFR calculated in the hospital laboratory system, the patients were divided into 3 groups as stage 3A, stage 3B and stage 4. The monocyte values in the hemograms of the patients were evaluated and the ratio of HDL to Monocyte/HDL in the lipid profile was calculated.

Ethical considerations: Written informed consent to participate in the study was obtained from all patients. The study was approved by the Ethics Committee of Diyarbakır Gazi Yaşargil Training and Research Hospital. (Issue-199; date: 30.09.2022)

Statistical analysis

Quantitative data are expressed as mean ± standard deviation (minimum-maximum), and categorical data are expressed as frequency (percentage). Data were analyzed using SPSS version 22.0. ShapiroWilk and Levene tests were used to determine the normality and homogeneity of the distribution, respectively. In statistical analysis, Oneway ANOVA was used for normal distribution, Kruskal-Wallis and post hoc

Table 2

	STAGE 3A	STAGE 3B	STAGE 4	*p*
AGE	59,2 ± 14,2	65,3 ± 12,7	64,5 ± 15,8	0,000
MHR	0,1571574 ± 0,0738	0,015877 ± 0,00731	0,015487 ± 0,00968	0,245

MHR: Monocyte HDL ratio, MHR values of the groups were statistically insignificant ($p = 0.245$).

Tukey HSD tests were used for data not normally distributed. $p < 0.05$ was considered statistically significant.

RESULTS

Patients aged ≥ 18 years and diagnosed with stage 3A, stage 3B and stage 4 CKD (with eGFR) in internal medicine or nephrology policlinics were included in this study. The mean age of the 632 patients included in our study was 63.4 ± 14.91(min:18max:98) and 305 (48.25%) of these patients were male and 327 (51.75%) were female. According to eGFR, 155 (24.5%) of the patients were stage 3A, 150 (23.8%) were stage 3B, and 327 (51.7%) were stage 4. Considering the comorbid conditions of the patients, 305 patients had DM, 586 patients had HT, and 429 patients had CAD. The distribution of patients' age, sex and comorbid conditions according to stages is summarized in table 1.

In the statistical study of the MHRs of the groups separated according to CKD stages, it was seen that there was no significant difference between the groups (*p*: 0,245) (Table 2 and fig. 1). There was statistical significance for gender and HT (*p*: 0.004 and p: 0.044, respectively) (Table 1).

DISCUSSION

CKD is a very important health problem. It is known that CKD patients progress rapidly to ESRD and need renal replacement therapy. Therefore, it is very important to prevent CKD and/or catch it in the early stages and stop the progression to ESRD. Concordantly, it is very important to know the definition of CKD and the risk factors for CKD, as well as to predict the progression of CKD stages.[1] MHR appears to be a new and useful marker of proinflammatory and anti-inflammatory indices. Monocytes and macrophages are cells that play an important role in the synthesis and release of proinflammatory and prooxidant cytokines.[9] It has been shown that HDL-C protects the endothelium against the destructive effects of LDL-C and prevents the oxidation of LDL-C.[10, 11] In this way, HDL-C acts as an anti-inflammatory agent and an antioxidant.[12-13]

In our literature review, we could not find a study between CKD stages and MHR. In this single-center retrospective study, we compared the MHR of 632 patients at different CKD stages. For this reason, we consider this study significant in terms of both the absence of similar studies in the literature and the number of patients examined.

Recently, studies have been published showing that MHR can be used in the early prediction of many chronic diseases or in the prediction of disease progression. In one study, MHR was evaluated while evaluating the stages of diabetic retinopathy and it was found to be significant in predicting the progression of retinopathy.[14] In another study, MHR was shown to play a prominent role in the prediction of subclinical carotid atherosclerosis in diabetics compared to non-diabetic populations.[15] In some studies, MHR was not found to be significant. In one study, MHR was compared between diabetic patients without nephropathy and healthy individuals, and no significant difference was found.[16-17] In another study, MHR was evaluated in patients with diabetic neuropathy and it was not found

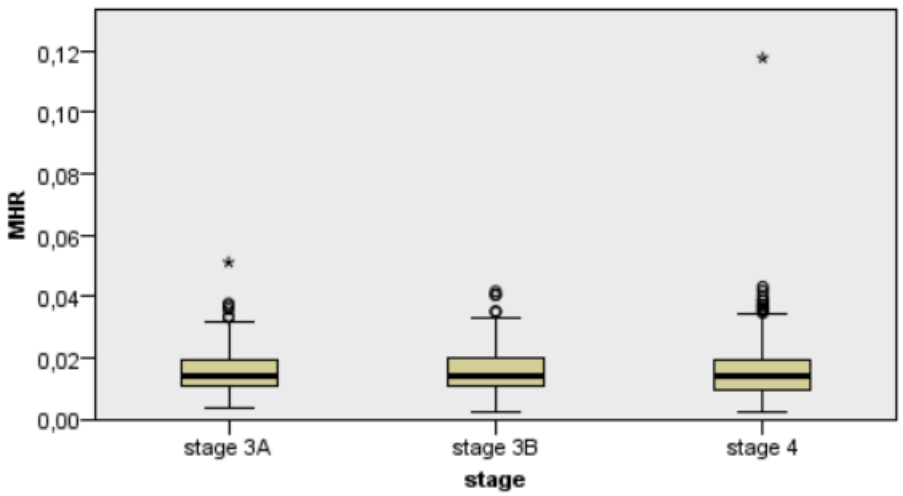

Fig. 1. Cruscal Wallis test comparison of CKD stages and MHR data

to be significant. [18] In this study, we compared stage 3A, stage 3B and stage 4 of CKD and we did not find any statistical difference between stages (p = 0.245). As a result of this study, we concluded that MHR is not affected by CKD stages.

Limitations

The most important limitation of the study is that it is a single center study. We recommend multicenter studies and further studies investigating the relationship between CKD stages and MHR with larger patient groups.

CONCLUSION

Authors' Contribution

Study Conception: İS, ÖFA, YY,; Study Design: İS, SK, YT,; Supervision: İS, EA, YT,; Materials: İS, ÖFA,; Data Collection and/or Processing: İS, ÖFA, YT,; Statistical Analysis and/or Data Interpretation: İS, ÖFA, SK,; Literature Review: İS, SK, EA,; Manuscript Preparation: İS, EA, SK and Critical Review: İS, SK, EA.

REFERENCES

1. Hebert LA, ve ark. Renoprotection: One or many therapies? Kidney Int 59:1211-1226, 2001.
2. Barter PJ, Nicholls S, Rye KA, et al. Antiinflammatory properties of HDL. Circ Res. 2004;95:764–772. 3. Negi G, Kumar A, Joshi RP, et al. Oxidative stress and Nrf2 in the pathophysiology of diabetic neuropathy: old perspective with a new angle. Biochem and Biophys Res Commun. 2011;408:1–5.
3. You S, Zhong C, Zheng D, Xu J, Zhang X, Liu H et al. Monocyte to HDL cholesterol ratio is associated with discharge and 3-month outcome in patients with acute intracerebral hemorrhage. J Neurol Sci 2017; 372: 157-61.
4. Karataş MB, Çanga Y, Özcan KS, Ipek G, Güngör B, Onuk T et al. Monocyte to high-density lipoprotein ratio as a new prognostic marker in patients with STEMI undergoing primary percutaneous coronary intervention. Am J Emerg Med 2016; 34(2): 240-4.
5. Canpolat U, Aytemir K, Yorgun H, Şahiner L, Kaya EB, Çay S et al. The role of preprocedural monocyte-to-high-density lipoprotein ratio in prediction of atrial fibrillation recurrence after cryoballoon-based catheter ablation. Europace 2015; 17(12): 1807-15.
6. Canpolat U, Çetin EH, Cetin S, Aydin S, Akboga MK, Yayla C et al. Association of Monocyte-to-HDL Cholesterol Ratio with Slow Coronary Flow is Linked to Systemic Inflammation. Clin Appl Thromb Hemost 2016; 22(5): 476-82.
7. Balta S, Celik T, Ozturk C, Kaya MG, Aparci M, Yildirim AO et al. The relation between monocyte to HDL ratio and noreflow phenomenon in the patients with acute ST-segment elevation myocardial infarction. Am J Emerg Med 2016; 34(8): 1542-7.
8. Ancuta P, Wang J, Gabuzda D. CD16 + monocytes produce IL-6, CCL2, and matrix metalloproteinase-9 upon interaction with CX3CL1-expressing endothelial cells . J Leukoc Biol 2006; 80(5): 1156-64.
9. Hessler JR, Robertson AL, Chisolm GM. LDL-induced cytotoxicity and its inhibition by HDL in human vascular smooth muscle and endothelial cells in culture. Atherosclerosis 1979; 32(3): 213-29.
10. Li XP, Zhao SP, Zhang XY, Liu L, Gao M, Zhou QC. Protective effect of high density lipoprotein on endotheliumdependent vasodilatation. Int J Cardiol 2000; 73(3): 231-6.
11. Parthasarathy S, Barnett J, Fong LG. High-density lipoprotein inhibits the oxidative modification of low-density lipoprotein. Biochim Biophys Acta 1990; 1044(2): 275–83.
12. Sözel Hasan, Avşar Esin, Alemdar Mustafa Serkan, Aydemir Mustafa Diyabetik süreçtemonosit/HDL kolesterol ve nötrofil/HDL kolesterol oranları. İzmir Eğitim ve Araştırma Hastanesi Tıp Dergisi, 2022;26(1):19 – 29
13. Solmaz, I., & Karahan, M. (2021). Monocyte count / HDL cholesterol ratio: A new marker in diabetic retinopathy . Annals of Medical Research, 28(2), 0258–0260.
14. Chen JW, Li C, Liu ZH, Shen Y, Ding FH, Shu XY et al. The role of monocyte to high-density lipoprotein cholesterol ratio in prediction of carotid intima-media thickness in patients with type 2 diabetes. Front Endocrinol (Lausanne) 2019; 10(4): 1– 11.
15. Karatas A, Turkmen E, Erdem E, Dugeroglu H, Kaya Y. Monocyte to high-density lipoprotein cholesterol ratio in patients with diabetes mellitus and diabetic nephropathy. Biomark Med 2018; 12(9): 953–9.
16. Onalan E. The relationship between monocyte to high-density lipoprotein cholesterol ratio and diabetic nephropathy. Pakistan J Med Sci 2019; 35(4): 1081–6.
17. Pençe H. H. , Aktaş H. Ş. Diyabetik Nöropatisi Olan Kişilerde Monosit/HDL Kolesterol Oranı ile Kardiyovasküler Risk Arasındaki İlişki. OTSBD. 2019; 4(4): 526-538.

Original Article
Internal Medicine
DOI: 10.56016/dahudermj.1225606

DAHUDER Medical Journal
e-ISSN: 2791-9250

Follow-up and treatment of patients with Common Variable Immune Deficiency: A single-center experience

Zeynep Yüksel, Ahmet Zafer Çalışkaner

Department of Internal Medicine Division of Oncology, University of Health Sciences, Istanbul Kartal Dr. Lutfi Kirdar City Hospital, Health Practice and Research Center, istanbul, Turkey

ABSTRACT

Objectives: Common Variable Immunodeficiency (CVID) is a primary immunodeficiency characterized by immunoglobulin production defect. Our study aimed to create awareness of primary immunodeficiency in adult patients, establish standard approaches for clinical follow-up of CVID patients, and reveal the clinical characteristics of CVID patients in our region.

Method: The study was conducted in patients with diagnosed and newly diagnosed CVID. The demographic and clinical characteristics of the patients and their treatment data were analyzed retrospectively and prospectively.

Results: Thirteen of our patients were female and 12 were male. The mean age at diagnosis of the patients was 30.32 (2-57) and the mean delay in diagnosis was 9.32 months (0-30). The most common clinical finding of our patients at the time of admission was an infection. Among the infections identified, 3 patients had URTI, 19 had LRTI, and 2 had gastroenteritis. In 16 of our patients, bronchiectasis was detected at the time of diagnosis, and in 1 during the follow-up period. In the examinations performed in terms of organomegaly, splenomegaly was found in 11 patients and hepatomegaly was found in 8 patients. When patients were screened for autoimmune disease, ITP and celiac were found in 2 patients at the beginning, while autoimmune thyroiditis was developed in 1 patient and SLE in 1 patient during follow-up. Our patients were given IVIG treatment at regular intervals. The number of reactions seen in a total of 421 IVIG infusions was two.

Conclusion: Primary immunodeficiencies should definitely be considered in patients with recurrent infections and resistance to antibiotic therapy. Patients should be followed according to established follow-up and treatment protocols in order to reduce and diagnose complications.

Keywords: CVID, primary immunodeficiency, follow-up and treatment protocols

Primary immunodeficiency is related to the defect in the development, function, or both of the immune system and may present as 200 different etiologies and clinical manifestations. Antibody-associated humoral primary immune system accounts for 65% of primary immunodeficiencies. Common variable immunodeficiency (CVID) is the most common of this group of diseases. CVID is a primary immunodeficiency disease characterized by defective production of immunoglobulins due to impaired B cell differentiation. [1]

The prevalence of the disease varies between 1:10,000 and 1:100,000 according to different populations, and both sexes are equally affected.

Received: *December 28, 2022;* ***Accepted:*** *January 7, 2023;* ***Published Online:*** *January 29, 2023*

How to cite this article: *Yüksel Z, Çalışkaner AZ. Follow-up and treatment of patients with Common Variable Immune Deficiency: A single-center experience. DAHUDER M J 2023,3(1):13-19. DOI: 10.56016/dahudermj.1225606*

Address for correspondence: *Zeynep Yuksel, M.D., Department of Internal Medicine Division of Oncology, University of Health Sciences, Istanbul Kartal Dr. Lutfi Kirdar City Hospital, Health Practice and Research Center, istanbul, Turkey. E-mail: dr_zeynepyuksel@hotmail.com.*

Typically, the age of onset of symptoms is after puberty and before the age of thirty. However, it has been reported that it has an early peak between the ages of 1-5. Although the disease is usually sporadic, familial transmission has been reported at a rate of 20%.[4]

It is very difficult to diagnose because CVID patients present with different symptoms and complications. Therefore, the diagnosis can often be made years later. The average delay in diagnosis was found to be 7.46 years in the European study conducted in CVID patient groups, and 8.9 years in the Italian study.[5-6] In a study conducted with 23 adult patients in our country, it was found that there was a delay in diagnosis of 8 years in women and 15 years in men.[7] The main reason for the delay in diagnosis is the lack of awareness of primary immunodeficiency in adult patients.

The diagnosis is made based on the clinical and laboratory features of the disease. While clinical examination may be normal in CVID patients, growth retardation and weight loss may be seen due to chronic disease. Findings such as oral candidiasis, gingivitis, tooth decay, cobblestone view on the posterior pharyngeal wall supporting chronic sinusitis, chronic perforated or scarred tympanic membrane image, clubbing in the fingers due to chronic lung disease can also be detected in the physical examination. In addition, lymphadenopathy, splenomegaly, arthritis, and skin findings related to the autoimmune disease are seen in some CVID patients.[8] In patients with CVID, routine laboratory tests such as complete blood count and urinalysis are usually not impaired. On the other hand, a decrease in globulin and/or total protein levels and lymphopenia can be detected in laboratory tests. Serum immunoglobulin levels are below two standard values for age.[9]

Another important problem in CVID patients is the follow-up process after diagnosis. Since clinical immunology has not progressed as much as basic immunology in our country, it has not been clarified who does or should do the clinical follow-up of adult immunodeficiency patients. There are no standard follow-up protocols for CVID patients both in our country and in the world. It is not clear how, how often, and for which problems these patients should be checked. This study, firstly, it was aimed to contribute to the formation of a protocol that will determine the clinical follow-up principles of CVID patients who are not under regular follow-up, and secondly, to reveal the clinical characteristics of CVID patients present in the region.

METHODS

The study protocol was approved by the Medical Ethics Committee of Necmettin Erbakan University. Written informed consent was obtained from all subjects included in the study. Twenty-five patients with CVID (13 females, 12 males; mean age, 36,60 ± 13,49 years) followed up by the Immunology and Allergy Department were included in the study.

The diagnosis of CVID was made according to the following criteria,

-Presence of all of the following criteria in a male or female patient who has a significant decrease in IgG levels (at least 2 SD below the mean values for age) and at least one of the low IgM or IgA levels,

1) Onset of immunodeficiency after 2 years of age,

2) Absence of isohemagglutinins and/or weak immune response to vaccines,

3) Exclusion of other causes of hypogammaglobulinemia.

Creation of follow-up documents

Standard guidelines and file forms that could be used in follow-up were not available for this group of patients. For this reason, a file format was prepared specifically for the study, containing information such as patient identity information, history, family history, disease history, previous examinations, examinations to be performed during diagnosis and follow-up, follow-up and treatment features, follow-up of complications, and treatment results.

Data collection

All records of all patients previously diagnosed with CVID were reviewed retrospectively. Files and epicrisis records from different clinics were collected. Data were processed into a CVID tracking file.

In addition, data collection was continued prospectively in the study. For this purpose, patients residing in Konya were called for control visits every 3 weeks, and those residing in distant places at least every 3 months. It was aimed to complete all the missing tests in the control visits and diagnose new complications. The general condition of the patients and changes in their quality of life was questioned. These inquiries were carried out by contacting the patients who did not or could not attend the control by telephone.

Informing the patient

Patients were interviewed about CVID disease.

Information was given about the cause, course, treatment, and complications of the disease. Family screenings of existing patients were performed. First-degree relatives were evaluated first. The possibility of disease in more distant relatives was explained to the patients, and it was aimed at people with complaints to apply to our clinic. In addition, the parents of pediatric patients diagnosed with CVID in the Department of Pediatric Immunology Allergy were evaluated for CVID in our clinic.

Determination of treatment standards

Certain standards have been introduced for immunoglobulin replacement therapies, which are administered intravenously. Intravenous Immunoglobulin (IVIG) doses are individualized. Clinical nurses were trained in infusion techniques. A standard IVIG infusion "order" was prepared and treatments were performed accordingly. An informed consent form was prepared for IVIG infusions, which are the basis of treatment, and an IVIG consent form was obtained from all patients. In addition, the patients were evaluated in terms of the need for prophylactic antibiotics. Prophylactic antibiotic therapy was initiated in patients with chronic lung disease or a history of frequent and prolonged infections.

Statistical analyses

Clinical and experimental data were analyzed using Statistical Package for Social Sciences for Windows version 21.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics for each variable were determined. Data were expressed as mean ± standard deviation or median and frequency.

RESULTS

Demographic findings and general characteristics

Of the 25 patients who participated in the study, 11 of them were adult patients diagnosed with CVID and still being followed by the Pediatric Immunology and Allergy Department, and 6 of them were adult CVID patients diagnosed in the Meram Medical Faculty Hospital Immunology and Allergy Diseases Department outpatient clinic. The remaining 8 patients were adult patients who were diagnosed with CVID and were not followed up in a specific clinic and were only receiving regular or irregular IVIG therapy. The mean age of diagnosis was 30.32 ± 13.84 years (10-57 years). The mean delay in diagnosis was 107.04 ± 95.61 months (0-360 months). Our patients were investigated with a pedigree in terms of consanguineous marriage. While 2 of our patients were siblings, consanguineous marriage was detected in 9 (36%) of our patients.

Findings at the time of diagnosis

When the admission symptoms of the patients were evaluated, it was determined that 92% of them presented with infection, 4% with treatment-resistant skin lesions, and 4% with diffuse lymphadenopathy. Among the infections identified, 3 patients had upper respiratory tract infections, 19 had lower respiratory tract infections, and 2 had gastroenteritis. When all patients were evaluated, two patients had concomitant chronic sinusitis, one patient had congestive heart failure, one patient had coronary artery disease, two patients had heart valve replacement history, one patient had the rheumatic disease, one patient had epilepsy, and one patient had psoriasis. In addition, one of our patients was followed up with hereditary hemorrhagic telangiectasia. Apart from these, one of our patients was under dialysis treatment due to chronic renal failure due to amyloidosis.19 of our patients (76%) had a history of recurrent pneumonia and hospitalization due to pneumonia at the time of admission. There was bronchiectasis in 16 (64%) of 25 CVID patients followed up in our clinic. In addition, one of our patients had a history of pneumonectomy for bronchiectasis.

When all patients who were followed up for CVID and participated in our study were examined in terms of admission complaints, the number of patients who applied for gastrointestinal complaints was 3 (12%). One of our patients was previously diagnosed with celiac due to malabsorption. At the time of admission, giardiasis was detected in 5 patients. Only 2 of the patients with giardiasis in stool analysis had gastroenteritis. When our patients were questioned in terms of inflammatory bowel disease, ulcerative colitis was found in one of our patients. 25 CVID patients participating in the study were screened for hepatitis A, hepatitis B, and hepatitis C at the time of diagnosis. While A and C positivity was not detected in any of the patients, hepatitis B positivity was detected in 2 patients who were being followed up by gastroenterology. In another patient who had been followed up in another center before, HBV DNA was found to be positive despite HBs-Ag negativity.

Hepatosplenomegaly, which is one of the complications that can be seen in CVID patients, was

checked with ultrasonography (USG) at the time of diagnosis. Splenomegaly was found in 11 (44%) of our patients, and hepatomegaly was found in 8 (32%) patients. Six patients (50%) with splenomegaly also had hepatomegaly. One of our patients had a history of splenectomy due to immune thrombocytopenia (ITP). Our patients were examined for malignancy at the time of diagnosis. There was no finding suggestive of malignancy in any of the patients. These data are summarized in Table 1.

Findings during follow-up

Our patients who participated in our study were scanned with high-resolution computed tomography (HRCT) for bronchiectasis at regular intervals and according to their symptoms. Newly developed bronchiectasis was detected in a patient with dyspnea, cough, and sputum complaints. In addition, patients were screened for organomegaly at regular intervals during their follow-ups. While it was observed that splenomegaly developed in a patient who did not have

Table 1. Demographic and clinical features of patients

	Age	Gender	Complaint	Findings at the time of diagnosis	Findings during follow-up
1	20	Male	URTI	-	Bronchiectasis
2	47	Male	URTI	Bronchiectasis, ITP, splenectomy	Surgeryfor sinusitis
3	26	Male	Gastroenteritis	Bronchiectasis	Splenomegaly
4	35	Female	LRTI	Bronchiectasis	--
5	53	Female	LRTI	Hepatomegaly	-
6	59	Female	Gastroenteritis	Bronchiectasis, Splenomegaly, Hepatomegaly, Celiac Disease	-
7	22	Female	LRTI	Bronchiectasis, Hepatomegaly	Improvement in hepatomegaly
8	27	Female	LRTI	Bronchiectasis, Splenomegaly	Pregnancy
9	52	Female	LRTI	Splenomegaly	-
10	60	Male	LRTI	Coronary artery disease	Atopy
11	27	Male	Skin lesion	Bronchiectasis, Splenomegaly, Hepatomegaly, Psoriasis	-
12	30	Female	LRTI	Splenomegaly	-
13	32	Male	LRTI	Bronchiectasis	-
14	25	Male	LRTI	Bronchiectasis, Splenomegaly, Hepatomegaly	Amyloidosis
15	21	Female	LRTI	Bronchiectasis	Thyroiditis
16	20	Female	URTI	-	SLE
17	30	Male	LRTI	Bronchiectasis, Splenomegaly, Hepatomegaly, CKD	
18	30	Female	LRTI	Bronchiectasis	Pregnancy
19	61	Male	LRTI	Bronchiectasis, Splenomegaly, Hepatomegaly	Cirrhosis
20	40	Male	LRTI	Splenomegaly	-
21	39	Female	LRTI	-	-
22	24	Male	LRTI	Bronchiectasis, Splenomegaly, Hepatomegaly	-
23	45	Male	LRTI	Bronchiectasis, Splenomegaly, rheumatoid arthritis	-
24	37	Female	LRTI	Bronchiectasis, Atopy	-
25	53	Female	LRTI	Coronary artery disease, lymphadenopathy	-

organomegaly at the beginning, hepatomegaly was observed to regress in the abdominal USG performed in the follow-up of a patient who was found to have hepatomegaly at the time of diagnosis.

Patients were screened for autoimmunity at regular intervals during follow-ups. Autoimmune thyroiditis was detected in one patient other than our patients with celiac and ITP diagnoses mentioned above. In addition, systemic lupus erythematosus was detected in one of our patients during follow-up.

Patients were screened for malignancy at regular intervals during follow-up, and none of them found any malignancy. Liver cirrhosis was observed in one of our patients, who was followed up abroad during the winter months and followed up by us in the summer, who had hepatitis B positivity at the time of diagnosis and was receiving antiviral treatment. During the follow-up, one of the patients applied to us with a general condition disorder, shortness of breath, pleural effusion, and diffuse edema. The patient with hypoalbuminemia was found to have 11 g of proteinuria in the 24-hour urinalysis. The patient was consulted with the nephrology outpatient clinic and a renal biopsy was planned. The biopsy result was compatible with amyloidosis. Except for this patient, no proteinuria was detected in any of the patients. One patient with chronic renal failure was not included in the screening.

Two of our patients who were followed up in our clinic due to CVID became pregnant during their follow-up. Our patients who continued IVIG treatment delivered without complications. The findings detected during the follow-up are summarized in Table 1.

URTI Upper respiratory tract infection, LRTI Lower respiratory tract infection, ITP Immune thrombocytopenia, CKD Chronic kidney disease

Data on treatments

IVIG replacement (400-600 mg/kg) was applied to all of our patients. While 25 patients (96%) were treated with IVIG at 21-day intervals, intravenous immunoglobulin replacement was applied to our patient with nephrotic syndrome at 15-day intervals.

Reactions were observed in 2 patients during IVIG infusions. Infusions were continued by controlling the reactions depending on the infusion rate with appropriate approaches (Table 2). The number of reactions seen in 421 infusions made during the study was 2.

DISCUSSION

As in the whole world, there is positive progress in health in our country, and as a result, life expectancy in chronic diseases is prolonged. In the past, children with immunodeficiency could not reach adulthood, so adult doctors had limited knowledge about this issue. However, the increase in the quality of treatment and care now necessitates adult physicians to have knowledge about this issue. Our study aimed to raise awareness among physicians of adult immunodeficiency diseases and to provide data for protocols that will set the follow-up and treatment of diagnosed patients to certain standards.

Antibody-associated humoral primary immunodeficiencies constitute 65% of primary immunodeficiencies, and CVID is the most common of this group of diseases. CVID is a primary immunodeficiency disease characterized by defective production of immunoglobulins due to impaired B cell differentiation. One of the most important problems in this group of patients is the delay in diagnosis. In our study, the mean age of symptom onset was 21.24 ± 17.18 years, while the mean age at diagnosis was 30.32 ± 13.84 years. The mean delay in diagnosis was 107.04 ± 95.61 months. In the literature, an average of 7.46 years in the European study on CVID patient groups, and 8.9 years in the Italian study were shown to be delayed in diagnosis.[5-6] In a study conducted with 23 adult patients in our country, it was found that there was a delay in diagnosis of 8 years in women

Table 2. Intravenous Immunoglobulin therapy administration protocol

	With infusion pump	With serum set
First 10 minutes	10 ml/hour	4 drops/minute
Next 20 minutes	20 ml/hour	8 drops/minute
Next 20 minutes	50 ml/hour	18 drops/minute
Next 60 minutes	100 ml/hour	32 drops/minute
The remainder of the infusion (Maintenance)	200 ml/hour	64 drops/minute

and 15 years in men.[7]

CVID is usually seen as sporadic cases. Familial transmission has been reported at a rate of 20% in the literature. [10] However, consanguineous marriage increases the incidence of the disease. 9 of our patients had consanguineous marriage and 1 patient was diagnosed with CVID as a result of family screening.

Pulmonary function tests and direct radiographs are limited in the follow-up of patients in terms of pulmonary complications. Pulmonary function tests can be useful in the follow-up and treatment evaluation of patients with chronic lung disease, and they can be applied at the diagnosis stage and when the clinical situation requires it. High-resolution lung tomography is very valuable in the evaluation of patients for bronchiectasis. However, there is no consensus on how often it should be applied. It is recommended to be drawn every 3-5 years from different sources and literature. [11-12] In addition, CVID patients are radiosensitive, there is insufficient knowledge about 'safe dose radiation', and imaging is needed for other pulmonary complications other than bronchiectasis. There are reservations about the follow-ups to be made with imaging. In our center, we evaluated our patients with HRCT every two years in terms of pulmonary complications, and those with symptoms in a shorter time.

Screening of patients for gastrointestinal complications is important because of the chance of early detection and treatment. Ultrasonography, endoscopy, parasite examinations, and liver enzyme monitoring are recommended. Endoscopy is one of the methods used in screening because of the increase in gastric cancer compared to the normal population. While some researchers argue that endoscopy should be performed every 2 years, there are also researchers who argue that the frequency of follow-up should be determined according to the initial findings.[13-14] It is recommended that USG be done annually, and parasite examination should be done during the routine examination. Since antibody production is insufficient in the follow-up of infections such as hepatitis B and C, viral load should be checked. In terms of nodular regenerative hyperplasia, another gastrointestinal complication, patients should be followed up with liver enzymes, and biopsy is recommended, especially if the ALP level is above 1.5 times for more than 6 months. [15] In our center, we screened patients with liver function tests at 6-month intervals and with abdominal USG at 2-year intervals.

Hemogram is usually sufficient for follow-up for hematological complications. Although it is not known at what intervals it should be done, it is recommended to be done every 3-6 months. Newly emerging symptoms and physical examination findings are important in terms of autoimmune diseases and malignancy. Examining autoantibodies at the diagnosis stage may help to explain the unknowns among CVID autoimmune diseases. It is recommended that patients who do not have additional findings in terms of malignancy should be screened according to the methods and intervals determined in the healthy population.[16-17] In line with these data, we screened our patients for autoimmunity every 6 months and for malignancy once a year.

While CVID patients had high mortality and morbidity in the past, today their life expectancy has increased considerably with appropriate treatment and follow-up. The mainstay of treatment is immunoglobulin replacement therapy, antibiotic therapy for infections, and supportive therapy for non-infectious complications. [18] The goal of immunoglobulin replacement therapy is to bring Ig levels to the normal range or to a value where infections are reduced. Ig half-life is 3 weeks on average and stable levels can be reached after 3-6 months of treatment. Intravenous and subcutaneous administration of IVIG therapy has been found to be equally effective and safe.[19] Although these treatments have been applied for a long time, there are differences between the centers in terms of application forms due to the side effects observed during the application. We created our own application protocol in our center and gave IVIG treatment to patients every 21 days.

As a result; CVID patients are patients who need close and special follow-up from the moment of diagnosis. There is a need for standardized treatment and follow-up protocols, especially in adult patients, in order to recognize and perhaps prevent complications in the early period, to keep the quality of life high, and to prolong survival. We think that the data and experience obtained from this study will be a source for such protocols.

CONCLUSION

None of the authors have any relationships with or financial interests in companies related to the findings of this work. None of the authors declare any conflicts of interest.

Contribution

Study Conception: AZÇ, ZY,; Study Design: AZÇ, ZY,; Supervision: AZÇ, ZY,; Materials: AZÇ, ZY,; Data Collection and/or Processing: AZÇ, ZY,; Statistical Analysis and/or Data Interpretation: AZÇ, ZY,; Literature Review: AZÇ, ZY,; Manuscript Preparation: AZÇ, ZY and Critical Review: AZÇ, ZY.

REFERENCES

1. Schroeder, HW, Jr. "Genetics of IgA deficiency and common variable immunodeficiency." Clin Rev Allergy Immunol 2000;19(2): 127-140.
2. Notarangelo, LD, A Fischer, RS Geha, JL Casanova, H Chapel, ME Conley, et al. "Primary immunodeficiencies: 2009 update." J Allergy Clin Immunol 2009;124(6): 1161-1178.
3. Conley, ME, J Rohrer, L Rapalus, EC Boylin and Y Minegishi. "Defects in early Bcell development: comparing the consequences of abnormalities in pre-BCR signaling in the human and the mouse." Immunol Rev 2000;178: 75-90.
4. Hammarstrom, L, I Vorechovsky and D Webster. "Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID)." Clin Exp Immunol 2000;120(2): 225-231.
5. Chapel, H, M Lucas, M Lee, J Bjorkander, D Webster, B Grimbacher, et al. "Common variable immunodeficiency disorders: division into distinct clinical phenotypes." Blood 2008;112(2): 277-286.
6. Quinti, I, A Soresina, G Spadaro, S Martino, S Donnanno, C Agostini, et al. "Longterm follow-up and outcome of a large cohort of patients with common variable immunodeficiency." J Clin Immunol 2007;27(3): 308-316.
7. Ardeniz, O, CB Avci, A Sin, G Ozgen, F Gunsar, N Mete, et al. "Vitamin D deficiency in the absence of enteropathy in three cases with common variable immunodeficiency." Int Arch Allergy Immunol 2008;147(1): 74-83.
8. Urschel, S, L Kayikci and U Wintergerst. "Common variable immundeficiency disorders in children: delayed diagnosis despite typical clinical presentation." J Pediatr 2009;(154): 888.
9. Conley, ME, LD Notarangelo and A Etzioni. "Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies)." Clin Immunol 1999;93(3): 190-197.
10. Cunningham-Rundles, C and C Bodian. "Common variable immunodeficiency: clinical and immunological features of 248 patients." Clin Immunol 1999;92(1): 34-48.
11. Bates, CA, MC Ellison, DA Lynch, CD Cool, KK Brown and JM Routes. "Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency." J Allergy Clin Immunol 2004;114(2): 415-421.
12. Wood, P, S Stanworth, J Burton, A Jones, DG Peckham, T Green, et al. "Recognition, clinical diagnosis and management of patients with primary antibody deficiencies: a systematic review." Clin Exp Immunol 2007;149(3): 410-423.
13. Daniels, JA, HM Lederman, A Maitra and EA Montgomery. "Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review." Am J Surg Pathol 2007;31(12): 1800-1812.
14. Agarwal, S and L Mayer. "Gastrointestinal manifestations in primary immune disorders." Inflamm Bowel Dis 2010;16(4): 703-711.
15. Resnick, ES, EL Moshier, JH Godbold and C Cunningham-Rundles. "Morbidity and mortality in common variable immune deficiency over 4 decades." Blood 2012;119(7): 1650-1657.
16. Notarangelo, LD, A Fischer, RS Geha, JL Casanova, H Chapel, ME Conley, et al. (2009). "Primary immunodeficiencies: 2009 update." J Allergy Clin Immunol 124(6): 1161-1178.
17. Agarwal, S and C Cunningham-Rundles. "Autoimmunity in common variable immunodeficiency." Curr Allergy Asthma Rep 2009; 9(5): 347-352.
18. Busse, PJ, S Razvi and C Cunningham-Rundles. "Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency." J Allergy Clin Immunol 2002;109(6): 1001-1004.
19. Chapel, HM, GP Spickett, D Ericson, W Engl, MM Eibl and J Bjorkander. "The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy." J Clin Immunol 2000;20(2): 94-100.

Original Article
Internal Medicine
DOI: 10.56016/dahudermj.1220959

DAHUDER Medical Journal
e-ISSN: 2791-9250

Evaluation of Interleukin 6 Levels in Severe COVID-19 Patients

Yildiz Okuturlar[1], İftihar Koksal[2], Yasemin Gundoğdu[1], Arzu Yuksel[3], Ozgur Okuturlar[4], Fadıl Havas[5], Cem Gun[6]

[1]Department of Internal Medicine, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey
[2]Department of Infectious Diseases and Clinical Microbiology, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey
[3]Department of Medical Biochemistry, Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey
[4]Department of Internal Medicine, Private Rami Hospital, , Istanbul, Turkey
[5]Department of Anesthesiology and Reanimation Acibadem Mehmet Ali Aydinlar University, Istanbul, Turkey
[6]Department of Emergency Medicine, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey

ABSTRACT

Objectives: Interleukin 6 (IL-6) plays a leading role in the proliferation and differentiation of immune cells. Level of IL-6 is manifestly increased under many inflammatory conditions, including cytokine release syndrome. We evaluated the IL-6 levels of patients who were hospitalized with the diagnosis of COVID-19.

Methods: In the study, the test results of 19 cases whose IL-6 levels were measured between March 11, 2020 and May 31, 2020 retrospectively. The inpatients in the covid service (Group 1) and the patients admitted to the Intensive Care Unit (ICU) of our hospital (Group 2) were compared and evaluated. In addition, patients with positive and negative RT-PCR test results were checked for IL-6.

Results: While 8 (Group 1) of 19 patients observed in the clinic were transferred to the ICU, 11 patients (Group 2) were observed in the covid service until their discharge. Group 1 IL-6 levels (median 34 pg/mL) and Group 2 IL-6 levels (median 116 pg/mL) were found to be high in both groups (p = 0,099). However, it was found to be significantly higher in patients with positive COVID-19 RT-PCR test (median 90.60 pg/mL) than in negative patients (median 29.90 pg/mL) (p = 0.018).

Conclusion: No significant difference in IL-6 levels between the patients who were monitored in the clinic and transferred to the ICU was found in this study. The significant difference between IL-6 levels among COVID-19 RT-PCR positive and negative patients reveals the importance of IL-6 level with regard to tocilizumab treatment in COVID-19 patients in cytokine storm.

Keywords: COVID-19, Interleukin 6, Cytokine Storm, Macrophage Activation Syndrome

The clinical spectrum of the new Coronavirus-19 (COVID-19) disease is wide, and in a preliminary study conducted by the World Health Organization in China 18.3% patients developed severe disease requiring oxygen while 6.1% patients developed intensive care. [1] The monitoring of prognostic markers in COVID-19 disease, which has undergone dynamic changes in treatment algorithms since the situation was defined as a pandemic, is important in terms of predicting the clinical course.

Received: *December 18, 2022;* ***Accepted:*** *January 25, 2023;* ***Published Online:*** *January 29, 2023*

How to cite this article: *Okuturlar Y, Koksal İ, Gundogdu Y, Yuksel A, Okuturlar O, Havas F, et al. Evaluation of Interleukin 6 Levels in Severe COVID-19 Patients. DAHUDER MJ 2023,3(1):20-25. DOI: DOI: 10.56016/dahudermj. 1220959*

Address for correspondence: *Ozgur Okuturlar, M.D., Private Rami Hospital, Cuma mah. Talimhane cad. No: 13 Rami, Eyüpsultan, 34055 Rami, İstanbul. Turkey. E-mail: ozokuturlar@gmail.com*

In this epidemic period, where immunological and thromboembolic events are common, it has been demonstrated in studies that proinflammatory cytokines such as tumor necrosis factor (TNF) receptor, interleukin-10 (IL-10), interleukin-8 (IL-8), interleukin-6 (IL-6) and interleukin 2 (IL-2R) are higher in severe patients. [2]

IL-6 is a cytokine that plays a role in the proliferation and differentiation of immune cells. In healthy individuals, the circulating level of IL-6 is very low (1-5 pg/mL), but increases prominently in many inflammatory conditions, including cytokine release syndrome. [3] It is known to be secreted by T cells, macrophages, endothelial cells, fibroblasts and monocytes. The thromboembolic process seen in the course of COVID-19 disease begins with the stimulation of tissue factor receptors involved in the coagulation cascade with the direct effect of IL-6 on monocytes. Another effect is that IL-6 activates the extrinsic coagulation cascade. [4]

In this study, we aimed to evaluate the relationship between the clinical course and other laboratory parameters of the degrees of IL-6 levels measured in severe COVID-19 patients.

METHODS

In this study, the IL-6 levels of 19 patients were evaluated and who were monitored with the diagnosis of COVID-19 in the pandemic service of Acıbadem Atakent Hospital, which operates as a pandemic hospital, were retrospectively analyzed. Results of the patients monitored in our clinic (Group 1) and those transferred to the Intensive Care Unit (ICU) of our hospital (Group 2) were compared and evaluated. Demographic data of the patients, COVID-19 Reverse Transcriptase- Polymerase Chain Reaction (RT-PCR) results in nose and throat swab samples, clinical course and laboratory findings were recorded retrospectively. In addition, patients with positive and negative RT-PCR test results were checked for IL-6; hemoglobin (Hb), PT, INR, D-dimer, urea, glomerular filtration rate (GFR), lactate dehydrogenase (LDH), C-Reactive Protein (CRP), Creatine Kinase (CK), troponin, fibrinogen, ferritin, Brain natriuretic peptide (BNP) upon admission- and values were compared between the groups. Additionally, the relationship between IL-6 level and other parameters was evaluated by using correlation analysis.

Statistics

The obtained data were analyzed using SPSS 24 software (IBM Corp, Armonk, NY). Descriptive statistical methods (mean, standard error, ratio) were used to evaluate study variables. In the analysis of data, Student's t test, Mann-Whitney U test, Chi-square test and Fisher exact test were used. A value of $p < 0.05$ was considered statistically significant. Ethics committee approval numbered 2020-08/20 was obtained for the study.

PT, INR, aPTT, D-dimer and fibrinogen tests were performed in Siemens CS 2000i device by coagulometric method from citrated plasma. Urea, LDH, CRP and BNP tests were performed by photometric method, where CK test was performed by enzymatic method from serum samples in Siemens Dimension device. Sodium, potassium and chlorine tests were performed using the ISE method from serum samples in the same device. Troponin, ferritin

Table 1. Data of Service (Group 1) and Intensive Care Unit (Group 2) Patients

	Group 1 (n = 11)		Group 2 (n = 8)		
	Frequency (n)	%	Frequency (n)	%	
Female	2	(18,2%)	3	(37,5%)	
Male	9	(81,8%)	5	(62,5%)	
Positive RT-PCR	4	(46,2%)	6	(75%)	
	Median		Median		*p*
IL-6	34 pg/mL		116 pg/mL		0,099
LDH	**239 U/L**		**365 U/L**		**0,045**
Exitus			2		

RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; IL-6: Interleukin-6; LDH: Lactate Dehydrogenase

and CK-MB mass tests and chemiluminescence (CLIA) method were performed from serum samples in Siemens Advia Centaur device. The measurement of IL-6 was performed in the Siemens Advia Centaur device using the CLIA method from a frozen serum sample.

RESULTS

While the female/male ratio in the clinic (Group 1) was 2/9 (18.2%/81.8%), the female/male ratio in the ICU (Group 2) was 3/5. (37.5/62.5%) No significant difference was found between the groups ($p > 0.05$). However, the number of male patients was higher in all critically sick patients (73.6%). The mean age of female patients (76.8 ± 4.9 years) was significantly higher than male patients (59.9 ± 13.9 years) ($p = 0.018$). The positive/negative PCR rate in the clinic was 4/7 (46.2%/53.8%), while the rate in the ICU was 6/2 (75%/25%). There was no significant difference between the groups in terms of test results. ($p > 0.05$). While the median IL-6 level was found to be high in both groups, 34 pg/mL in the clinic, 116 pg/mL in the ICU, the difference between them was not statistically significant. ($p > 0.05$). When ICU and clinical patients are compared, when the examinations performed upon admission are evaluated, there is no significant difference between leukocytes, neutrophils, lymphocytes, monocytes, hemoglobin, platelets, MPV, D dimer, CRP, troponin, fibrinogen, ferritin, CK, creatinine, calcium, albumin and glucose. However, LDH level was found to be significantly higher in patients who went to the ICU upon admission (365 U/L) compared to patients monitored in the clinic (239 U/L) ($p = 0.045$). Two patients transferred to the ICU have passed away and the RT-PCR results of these patients were positive. (Table 1).

Since there was no significant difference between group 1 and group 2 IL-6 levels, patients with positive and negative RT-PCR tests were divided into 2 groups and examined. A significant difference was found between IL-6, Hb, PT, INR, urea, GFR, LDH and BNP levels between positive and negative test results ($p < 0.05$). When D-dimer, CRP, CK, troponin, fibrinogen and ferritin values were evaluated, no significant difference was found between the groups (Table 2).

When the correlation between IL-6 level and other parameters in all patients was examined, it was noticed that IL-6 level was negatively correlated with monocytes (r = -730; p = 0.005) and positively correlated with CK level (r = 0.518; $p = 0.04$). ($p < 0.05$). (Table 3)

Table 2. Comparison of IL-6 and Other Parameters of Patients According to RT-PCR Test Results

	RT-PCR negative					RT-PCR positive					
	Mean	SD	Min	Max	Median	Mean	SD	Min	Max	Median	p
IL-6 (pg/mL)	37.60	27.40	8.18	93.18	29.90	225.48	366.54	5.70	1231.00	90.60	**0.018**
Hb (g/dL) First day	10.71	2.45	5.6	14.4	10.80	13.08	1.20	11.3	14.9	12.85	**0.010**
PT (second)	19.50	12.65	12.9	50.4	14.65	12.46	1.26	11.6	15.9	12.15	**0.003**
INR	1.62	1.09	1.1	4.5	1.20	1.06	0.13	1.0	1.4	1.00	**0.002**
D-dimer(ng/mL)	5.1067	7.47	0.19	20.00	2.60	14550	1.98	0.49	6.31	0.8750	0.245
Üre (mg/dL)	46.76	27.70	17	104	37	20	10.06	9.00	38.00	17	**0.032**
GFR (mL/Minute)	67.41	20.33	34.9	97.5	66.40	92.90	23.02	47.4	116.0	97	**0.030**
LDH (U/L)	252.00	87.36	174.0	362.0	214.50	349.67	100.18	239.0	568.0	357	**0.045**
CRP (mg/dL) First day	13.36	10.15	3.16	29.87	10.24	10.02	3.46	5.37	16.88	9.50	0.775
CK (U/L)	225.86	342.96	4.0	989.0	106	566.88	496.34	76.0	1156.0	519.50	0.165
Troponin (ng/mL)	0.16217	0.29	0.014	0.753	0.06	0.06	0.07	0.006	0.210	0,05	0.518
Fibrinojen(mg/dL)	489	319.17	257	853	357	514.25	82.65	405.0	645	486	0.414
Ferritin (ml/ng) First day	1356	1419.87	352	2360	1356	644.43	496.53	116.0	1480	450	0.558
BNP (pg/mL)	1925	1566.77	313	4099	1475	433.14	652.31	7.0	1807	90	**0.042**

RT-PCR: Reverse Transcriptase-Polymerase Chain Reaction; IL-6: Interleukin-6; Hb: Hemoglobin; PT: Prothrombin Time; INR: International Correction Rate; GFR:Glomerular Filtration Rate; LDH:Lactate Dehydrogenase; CRP:C-Reactive Protein; CK: Creatine Kinase; BNP: Brain Natriuretic Peptide; SD: Standart Deviation

Table 3. The Relationship of IL-6 with Other Parameters

Interleukin 6 and	r value	p value
Monosit	-,730**	**0,005**
D-dimer	-0,086	0,771
Urea	-,681*	**0,010**
K	-,499*	**0,035**
CRP	0,189	0,439
CK	,518*	**0,048**
Troponin	0,102	0,740
Fibrinogen	0,064	0,853
Ferritin	0,133	0,732
BNP	-0,014	0,966

IL-6: Interleukin-6; K: Potassium; CRP: C-Reactive Protein; CK: Creatine Kinase; BNP:Brain Natriuretic Peptide

DISCUSSION

The condition defined as Macrophage Activation Syndrome (MAS) due to excessive cytokine secretion in infectious sepsis can also be seen in the course of COVID-19. Acute respiratory distress syndrome (ARDS) also occurs as a result of excessive cytokine secretion, and studies have shown that IL-6 level is associated with prognosis in Acute respiratory distress syndrome (ARDS), and its use in clinical practice is recommended. [5] It was stated in a study by Herold et. al that IL-6 level can be associated with prognosis in COVID-19 disease and that the risk of respiratory failure is 92% (22 times higher than normal) in patients with IL-6 level > 80 pg/mL.[6] In this group with high IL-6 levels, the median time for mechanical ventilation was found to be 1.5 days (min0-max4). In our study, while the median IL-6 level was 116 pg/mL in our ICU patients, it was found to be 34 in our clinic patients, but there was no significant difference between them. One of the reasons for this is the low number of patients, while another reason may be that the patients whose IL-6 levels are evaluated in the service receive high oxygen or BIPAP support, that is to say, that they are in the course of severe disease.

When the patients with negative and positive RT-PCR test results were compared, a statistically significant difference was found between IL-6 levels. This may be due to the fact that the viral load is higher in patients with a positive test, thus severe disease burden. In the study of Chen *et al*., COVID-19 patients with higher viral load had a more severe course, and ARDS was more common in this group of patients.[7] If we associate viremia with a positive RT-PCR test, it can be suggested that the burden of disease and thus the risk of MAS may be higher in patients with a positive test result. In the treatment guideline updated by the Turkish Ministry of Health on November 7, 2020, the use of tocilizumab, an anti-IL-6 receptor monoclonal antibody, is recommended in patients who have developed MAS.[8] Tocilizumab (400 mg/day) was administered to 5 patients with positive RT-PCR results in our clinic, and the mean IL-6 level was 347.18 pg/mL in these patients.

When we examine these cases, in which we applied tocilizumab, one by one; The first case is a 32-year-old male patient without any comorbidities, who applied to the emergency department with difficulty in breathing 1 week after the onset of COVID-19 symptoms. The patient, who had completed plaquenil and azithromycin treatments at home, was hospitalized because his room air saturation was 92%. The IL-6 level of the patient, whose saturation decreased to 88 during the follow-up and was given oxygen support with a reservoir mask, was found to be 108 pg/mL on the second day of hospitalization. Tocilizumab was administered for 2 consecutive days, and the patient was monitored in the clinic. 2 days upon application, his IL6 level decreased to 17.3 pg/mL, and the patient was discharged without any complications, as his general condition improved. In the second case; a 70-year-old male patient applied to the emergency department with fever, difficulty of breathing and tachypnea. He had hypertension and type 2 diabetes. Favipiravir and plaquenil treatments were applied. He was transferred to the ICU and intubated due to desaturation while he was being monitored with a non-invasive mechanical ventilator on his 3rd day in the clinic. IL-6, measured on his 6th day of monitoring in the ICU, was 161 pg/mL, and tocilizumab was administered for 2 consecutive days. The patient, who was admitted to the clinic after 29 days of treatment in the ICU, was discharged without complications.

The third case is a 60-year-old male patient who was referred to the hospital from another center and had no comorbidities other than essential hypertension. After completing the favipiravir treatment, he was transferred to the ICU due to desaturation and worsening in his clinical condition despite Bipap support on his 2nd day of monitoring in the clinic. On the 2nd day of his hospitalization, IL-6 was detected

as 1231 pg/mL, the first dose of tocilizumab was administered in the clinic, the treatment continued in the ICU the next day. Immune plasma therapy was applied to the patient whose clinical condition did not improve. The patient, who was monitored with non-invasive mechanical ventilation, was transferred to the clinic one week later and was discharged without complications.

In the fourth case; plaquenil and azithromycin treatments were given to a 60-year-old male patient with coronary artery disease and hypertension. On his 2nd day of hospitalization in the clinic, he was transferred to the ICU and intubated. On the 3rd day of monitoring in the ICU, IL-6 was 163 pg/mL. The patient, who was administered tocilizumab for 2 days, was extubated after 1 week of treatment in the ICU, and was discharged without complications.

In the fifth case, a 49-year-old male patient with a known history of hypertension was transferred to the ICU on his 5th day of monitoring in the clinic because of desaturation despite Bipap support. Plaquenil and favipiravir treatments were administered. The IL-6 level of the patient, who was monitored in the ICU as intubated, was found to be 73.2 pg/mL on his 4th day in the ICU, and tocilizumab was administered for 2 days. The patient, whose treatment continued for 9 days in the ICU, was taken to the clinic after clinical improvement, and was discharged without complications after 5 days of monitoring in the clinic.

One of the most important cytokines triggering MAS is IL-6, and its high levels are known to cause ARDS by damaging the lung vascular endothelium, at the same time, there are studies showing that IL-6 plays a remodeling and anti-inflammatory role in the lung. Due to the two contrasting features, the timing of administration of anti-IL-6 (tocilizumab) therapy is critical. Therefore, successive IL-6 monitoring may be clinically important.[9]

In our study, the frequency of male patients (73.6%) in critically ill patients was higher than female patients (26.4%). Likewise, in the meta-analysis conducted by Barek and his friends on 10,000 patients, it was shown that the prevalence of male gender was significantly higher at 62.8% in critically ill patients.[10] The average age of female patients being 76.8 years, may indicate that the course of COVID-19 is more severe, especially in postmenopausal women. Although mortality is higher in male gender in the general population, it has been shown in the study of Cagnacci and his friends that COVID-19 is more mortal than the premenopausal age group due to decreased estrogen level in postmenopausal women.[11]

Successive monitoring of hematological and biochemical parameters, which are important in the course of critically ill patients, is substantial. However, there is a need for parameters that can give an idea about the course of the patients at the time of application. The fact that only the LDH level was different in our study may be a significant indicator. As a result of the analysis performed by Li and his friends in Wuhan, a significant correlation was shown between LDH and provincial mortality at the time of admission, and the risk of going to the ICU and mortality was calculated to be twice as high in patients with an LDH level higher than 445 U/L.[12] In the light of studies like this, we can deduce that LDH is a cheap and fast-resulting test in many health units, so its use as a prognostic marker in the course of COVID-19 is a cost-effective test. Furthermore, CK can be considered as one of the parameters to be followed in patients with cytokine storm, since IL-6 level is significantly positively correlated with CK.

CONCLUSION

The clinical course of COVID-19 disease varies, and it has a wide spectrum from asymptomatic disease to severe pneumonia and MAS. IL-6 has been shown to occur more likely in severe patients, and treatment strategies for IL-6 have been used in some patients. Anti-cytokine treatment algorithms vary between countries, and more detailed studies on the application time and indications of tocilizumab treatment will contribute to similar applications. Consecutive monitoring of IL-6 level as a prognostic marker is valuable in the pandemic period where the patient burden is accumulated, therefore, the accuracy of triage is substantial.

Authors' Contribution

Study Conception: YO, IK,; Study Design: YO, IK,; Supervision: YO, IK,; Materials: YG, AY, FH,; Data Collection and/or Processing: YG, AY, FH,; Statistical Analysis and/or Data Interpretation: YO, YG,; Literature Review: YO, CG, YG, OO,; Manuscript Preparation: YO, CG, YG, OO and Critical Review: IK, YO.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Acknowledgements

We are grateful to all treating physicians in our center for collaboration and the data collection.

Financing

There is no source of financial support or funding.

REFERENCES

1. Zhang J, Hao Y, Ou W, Ming F, Liang G, Qian Y et al. Serum interleukin-6 is an indicator for severity in 901 patients with SARS-CoV-2 infection: a cohort study. J Transl Med. 2020;18(1).
2. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;m1091.
3. Galván-Román J, Rodríguez-García S, Roy-Vallejo E, Marcos-Jiménez A, Sánchez-Alonso S, Fernández-Díaz C. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: An observational study. J Allergy Clinic Immunol. 2021;147(1):72-80.e8.
4. Narazaki M, Kishimoto T. The Two-Faced Cytokine IL-6 in Host Defense and Diseases. Int J Mol Sci. 2018;19(11):3528.
5. Swaroopa D, Bhaskar K, Mahathi T, Katkam S, Raju Y, Chandra N et al. Association of serum interleukin-6, interleukin-8, and Acute Physiology and Chronic Health Evaluation II score with clinical outcome in patients with acute respiratory distress syndrome. Indian J Crit Care Med. 2016;20(9):518-525.
6. Herold T, Jurinovic V, Arnreich C, Hellmuth J, von Bergwelt-Baildon M. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. 2020;146(1):128-136
7. Chen W, Lan Y, Yuan X, Deng X, Li Y, Cai X. Detectable 2019-nCoV viral RNA in blood is a strong indicator for the further clinical severity. Emerg Microbes Infect. 2020;9(1):469-473.
8. Antisitokin-Antiinflamatuar Tedaviler, Koagülopati Yönetimi . Covid19.saglik.gov.tr. 2022. https://covid19.saglik.gov.tr/TR-66341/antisitokin-antiinflamatuar-tedaviler-koagulopati-yonetimi.html (accessed February 2022)
9. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta. 2011;1813(5):878-888.
10. Barek M, Aziz M, Islam M. Impact of age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: A meta-analysis with 55 studies and 10014 cases. Heliyon. 2020;6(12):e05684.
11. Cagnacci A, Xholli A. Age-related difference in the rate of coronavirus disease 2019 mortality in women versus men. Am J Obstet Gynecol. 2020;223(3):453-454.
12. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-118.

Case Report
Geriatrics and Family Medicine
DOI: 110.56016/dahudermj.1201319

DAHUDER
Medical Journal
e-ISSN: 2791-9250

Sudden Hairloss and COVID-19

Hilal Heybeli[1], Ozden Gokdemir[2]

[1]*Department of Geriatrics, Ankara City Hospital, Ankara, Turkey*
[2]*Department of Family Medicine, İzmir University of Economics Faculty of Medicine, İzmir, Turkey*

ABSTRACT

A woman, 51 years old with known hypothyroidism, was admitted to the emergency service because of postoperative complaints of nausea, vomiting, and jaundice. The patient's imaging revealed pleural effusion, compression atelectasis in the right lung, and lesions compatible with type 2 hydatid cysts in the liver; therefore, PAIR (Puncture, Aspiration, Injection, Reaspiration) was planned, and she was admitted to the internal medicine service. After this, the routine COVID PCR, taken before the interventional procedure, was found positive. During the patient's follow-up, there were no indications of respiratory failure brought on by a COVID infection. Although her vitals were steady, it was noted that she had an intense headache, and frequent and severe hair loss from night to morning on the third day of hospitalisation due to a contagious infection. There are few photos about similar cases. This case also important to be recognized as a symptom/complication of COVID-19 to be managed.

Keywords: COVID-19, sudden hair-loss, symptom

A common type of hair loss known as telogen effluvium (TE) is defined by diffuse hair shedding and is brought on by the hair's early transition into the telogen phase. Triggering factors include systemic chronic conditions, stressors, treatments, dietary deficiencies, and surgical intervention. Hair loss begins 3 months after the triggering event and typically lasts for six months (acute TE). When the time frame for hair loss exceeds 6 months, there is also a chronic form of TE.[1] Wise recently reported that *"The cohort consisted of 486 149 confirmed SARS-CoV-2 infected individuals who were not hospitalised, matched with a control group of 1.9 million individuals who had no known coronavirus infection. Twelve weeks after their initial SARS-CoV-2 infection, those who tested positive for the virus reported at least one of 62 symptoms more frequently than those who had not. Anosmia (6.49 (95% confidence interval 5.02 to 8.39), hair loss (3.99 (3.63 to 4.39), sneezing (2.77 (1.40 to 5.50), ejaculation difficulty (2.63 (1.61 to 4.28), decreased libido (2.36 (1.61 to 3.47), and shortness of breath (2.20 (1.57 to 3.08) were the symptoms with the highest adjusted hazard ratios. A hoarse voice, fever, and chest pain were additional typical symptoms".*[2] In Turkey, Aksoy *et al* also revealed that in 3 months duration "COVID-19 associated TE (CATE)" was an average of 53.76 (± 23.772) days after COVID-19 RT-PCR positivity. In this study, the three risk factors for CATE were: being a woman, being diagnosed with hypertension, and having respiratory symptoms during COVID-19.[3]

Received: *November 9, 2022;* ***Accepted:*** *January 8, 2023;* ***Published Online:*** *January 29, 2023*

How to cite this article: *Heybeli H., Gokdemir O. Sudden Hairloss and COVID-19. DAHUDER M J 2023,3(1):26-31. DOI: 10.56016/dahudermj.1201319*

Address for correspondence: *Ozden GOKDEMİR, M.D., Department of Family Medicine, İzmir University of Economics Faculty of Medicine, İzmir, Turkey. E-mail: gokdemirozden@gmail.com*

Table 1.

	April 08.2021	April 26.2021
HGB: Hemoglobin(g/dl)	9,4 (12-15,6)	9,2
HCT: Hematocrit(%)	30,7 (35,5-45,5)	31,6
WBC: White Blood Cell (µ/mm^3)	3600(3900-10200)	5290
Ne: Neutrophil (10^3/mm^3)	2330 (1500-7700)	2440
LY: Lymphocyte (10^3/mm^3)	890 (1100-4500)	1940
PLT: Platelet (%)	409000 (150000-400000)	364000
Glucose (mg/dl)	134 (70-99)	143
HbA1c(%)	5,4 (10.04.2021)	
Urea (mg/dl)	9 (19-49)	17
Creatinine (mg/dl)	0,43 (0,5-1,1)	0,57
eGFR(ml/min/1.73m^2)	120 (> 90)	109
t.protein (g/l)	69 (57-82)	65
Albümin (g/l)	37 (32-48)	35
CK (U/L)	34 (33-211)	22
AST (U/L)	827 (< 35)	270
ALT (U/L)	721 (< 50)	232
ALP (U/L)	166 (42-98)	153
GGT (U/L)	141 (< 38)	220
LDH (U/L)	318 (120-246)	251
Amylase (U/L)	59 (30-118)	53
Lipase (U/L)	50 (12-53)	47
Total bilirubin (mg/dl)	12,6 (0,3-1,2)	1,8
Direct bilirubin (mg/dl)	8,4 (< 0,3)	1,3
Calcium (mg/dl)	9,2 (8,7-10,4)	9,3
Magnesium (mg/dl)	1,8 (1,3-2,7)	1,7
Phosphorus (mg/dl)	3,5 (2,4-5,1)	4,8
Sodium (mEq/L)	137 (132-146)	138
Potasium (mEq/L)	4,4 (3,5-5,5)	4,2
Procalsitonine (µg/L)	0,47 (< 0,16)	0,13
CRP (g/L)	0,01 (0-0,005)	0,00
Covid-19 reverse transkriptaz PCR	Positive (April 09.2021)	
PT (sn)	12,4 (9,8-14)	11,5
Protrombin activity (%)	85,5 (70-130)	109
INR	1,1 (0,8-1,2)	1
Aptt (sn)	24 (21-32)	24,2
Fibrinogen (g/L)	1,9 (1,7-4,2)	3,41
d-dimer (mg/L)	1,14 (< 0,55)	0,41
Free T4 (ng/dl)	1,13 (0,89-1,76)	
TSH (mU/L)	4,61 (0,55-4,78)	
Ferritin (µg/L)	1264 (10-291)	107
Sedimentation (ESR) (mm/hour)	39 (0-20)	
Pheripheric smear	Leukocyte compatible, leukopenic, hypochromic, atypical cells absent, anisopoikikilocytosis, platellet compatible is the formula.	
HbsAg	0,1 (negative) (0-0,99)	
AntiHbs	< 3,1 (negative) (0-10)	
AntiHCV	0,05 (negative) (0-0,8)	
AntiHIV	0,05 (non reactive) (0-0,999)	
IL-6 (pg/ml)	7,4 (0-4,4)	
Troponine I H (ng/L)	< 2,5 (< 45)	
Miyoglobine (µg/L)	21 (<110)	
Haptoglobine (g/L)	0,843 (0,3-2)	

Fig. 1. The amount of hair loss till morning

CASE REPORT

Our case is a 51-year-old with known hypothyroidism (the only drug she uses regularly is levothyroxine 100 mcg for 4 days, 75 mcg for 3 days) and liver cyst hydatid (she was treated with albendazole 3 weeks earlier, but this discontinued due to gastrointestinal symptoms and intolerance 1.5 months ago). The operated patient applied to the emergency department with complaints of nausea, vomiting, and jaundice. PAIR (Puncture, Aspiration, Injection, Reaspiration) was planned after the patient's imaging revealed pleural effusion, compression atelectasis in the right lung, and lesions compatible with type 2 hydatid cysts in the liver, and she was admitted to the internal medicine service.

She was admitted to the COVID service non-symptomatically in terms of COVID on April 10, 2021, after a positive result was found for the routine COVID PCR taken before the interventional procedure During the patient's follow-up, no indications of respiratory failure brought on by a COVID infection were seen. Her vitals remained steady (the labaratuary results are shown in Table 1). An intense headache, frequent, and severe hair loss from night to morning were noted on the third day of the patient's hospitalisation due to a contagious infection. (Figs. 1, 2, 3 and 4) After ruling out other potential causes, and the possibility of a e COVID infection causing telogen effluvium was considered (for example, through vitamin deficiencies). A dermatologist was consulted, and further testing was advised. The patient provided her fully informed consent.

DISCUSSION

Not only in Turkey, but across all countries, whether developed or not, it is confirmed that COVID-19 cases represent a challenge among the whole population range. A limitation of the study is the use of routinely coded healthcare data, which may understate the true burden of symptoms endured by people with long COVID. Due to the extremely limited community testing for SARS-CoV-2 during the pandemic's initial surge, there is also the possibility of classification bias. [2]

As COVID 19, in December 2019, the ongoing COVID-19 pandemic added to these difficulties.

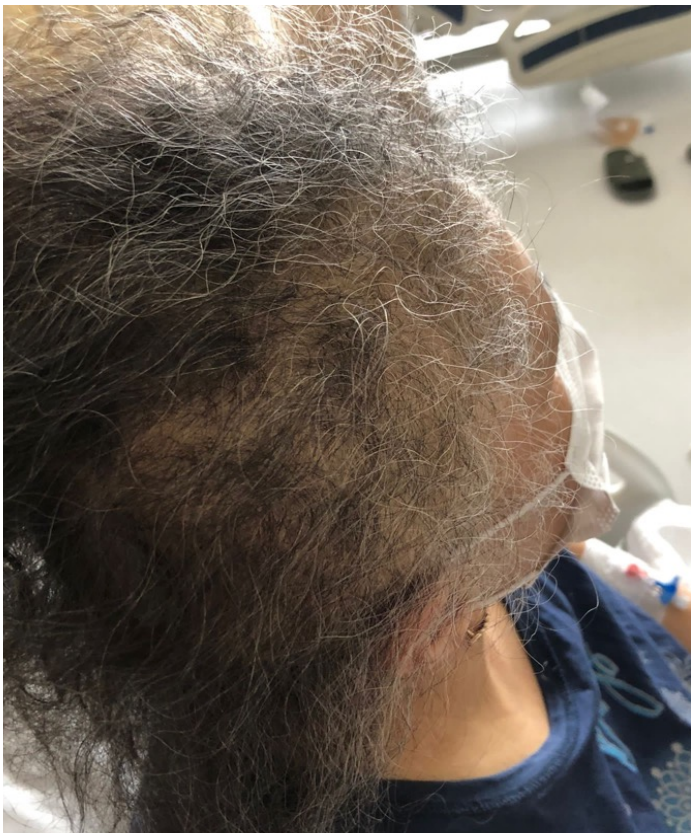

Fig. 2. **The inspection for the first day of sudden hairloss**

Fig. 3. **Inspection of scalp (left side)**

As a result, it must be presumed that every patient admitted has come into contact with COVID-19, whether child or adult. 4 According to D'Amico and colleagues' research, between 2% and 50% of patients with COVID-19 have diarrhea. Protein is used by COVID-19, ACE2 (angiotensin-converting enzyme 2), and TMPRSS2 (a serine protease)., It is known that ACE2, and the small intestine and the lungs both contain, the epithelium also expresses it. ACE2 is expressed in the upper portions of the oesophagus and the large intestine. [5] Low frequencies of skin conditions were reported in the early studies from COVID-19 patients in Central China. Only 0.2% of the 1099 confirmed cases in Wuhan had cutaneous symptoms. The fight against the most recent outbreaks of the pandemic has increased dermatologist involvement, and interest in the cutaneous symptoms of SARS-CoV-2 infection. [6] An example is the effort to understand "hair loss", and alopecia and COVID-19 tract. Androgens are involved in COVID-19 through a variety of pathways. Cellular coreceptor androgen-regulated TMPRSS2 protease is necessary for SARS-CoV-2 infection, as this enzyme primes the viral spike protein. [7] Given that androgens suppress the immune system, another connection is the androgen-driven immune modulation. Males predominate among adult COVID-19 patients, in fact. [8] Geographic COVID-19 distribution may be determined by genetic factors. 3-hydroxysteroid dehydrogenase-1, which is responsible for converting dehydroepiandrosterone into active and potent androgens, is encoded by the HSD3B1 gene's adrenal-permissive phenotype. According to the 1000 Genomes Project, the populations of Italy and Spain have the highest frequencies of the HSD3B1 allele. [9] These differences may be responsible for "hairloss" being observed in some cases but not others. [10]

Ohyama *et al* revelaed that "…using PubMed to conduct a narrative review on the prevalence, associated comorbidities, disease characteristics, and therapies for hair loss following SARS-CoV-2 infection (HLASCI). 28 articles were found using two search strings. It should be noted that the majority of the literature found on COVID-19 sequelae mentioned the emergence or occurrence of hair loss. The onset or exacerbation of telogen effluvium (TE), anagen effluvium, androgenetic alopecia (AGA), and alopecia areata (AA) have all been reported as potential underlying mechanisms for HLASCI, which is thought to consist of a heterogeneous population. Acute TE is one of these and is thought to be the main contributor to HLASCI, with COVID-19 therapy and TE improvement being important for

Fig. 4. Inspection of scalp (right side)

HLASCI management. It has also been suggested that COVID-19 and AA exacerbation are related.". 11

CONCLUSION

In conclusion, COVID-19 may be linked to CATE and other types of alopecia. Because COVID-19 hair loss typically begins a few months after infection, SARS-CoV2 may occasionally be incorrectly identified as the cause. Patients may experience excessive anxiety as a result of this misdiagnosis and may undergo unnecessary tests or treatments. It is important that the COVID-19 spectrum that affects the hair is clearly understood by physicians.

Authors' Contribution

Study Conception: OG, HH,; Study Design: OG, HH,; Supervision: OG,; Materials: HH,; Data Collection and/or Processing: HH,; Statistical Analysis and/or Data Interpretation: OG, HH,; Literature Review: OG, HH,; Manuscript Preparation: OG, HH and Critical Review: OG.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

Ethical approval statement

Patient' consent has been taken.

Acknowledgements

All the authors would like to thank Simon Mumford for English Language editing.

REFERENCES

1. Rivetti N, Barruscotti S. Management of telogen effluvium during the COVID-19 emergency: Psychological implications. Dermatol Ther. 2020;33(4):19–20.
2. Wise J. Long covid: Hair loss and sexual dysfunction are among wider symptoms, study finds. BMJ. 2022;378:o1887.
3. Aksoy H, Yıldırım UM, Ergen P, Gürel MS. COVID-19 induced telogen effluvium. Dermatol Ther. 2021;34(6):2–6.
4. Gokdemir O, Kavlakci M. Acute Diarrhea and Dehydration at Childhood During Pandemic. Turkish J Fam Med Prim Care. 2021;15(1):194–201.
5. D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea During COVID-19 Infection: Pathogenesis, Epidemiology, Prevention, and Management. Clin Gastroenterol Hepatol. 2020 Jul;18(8):1663-1672. doi: 10.1016/j.cgh.2020.04.001.
6. Wollina U, Karadağ AS, Rowland-Payne C, Chiriac A, Lotti T. Cutaneous signs in COVID-19 patients: A review. Dermatol Ther. 2020 Sep;33(5):e13549. doi: 10.1111/dth.13549.