ORIGINAL ARTICLE

JCD Journal of Cosmetic Dermatology   WILEY

Evaluation of patients with telogen effluvium during the pandemic: May the monocytes be responsible for post COVID-19 telogen effluvium?

Sema Koç Yıldırım MD [ID] | Ece Erbağcı MD [ID] | Neslihan Demirel Öğüt MD [ID]

Department of Dermatology and Venereology, Uşak University Training and Research Hospital, Uşak, Turkey

Correspondence
Sema Koç Yıldırım, Department of Dermatology and Venereology, Uşak University Training and Research Hospital, Uşak 64200, Turkey.
Email: semakocyildirim@gmail.com

Abstract

Introduction: Telogen effluvium (TE) is one of the causes of non-scarring hair loss that occurred commonly 2–3 months after a triggering factor. It was reported that the incidence of TE increased during the COVID-19 (coronavirus disease 2019) pandemic. However, to date, there is no study evaluating the status of COVID-19 before the onset of hair loss in patients with TE. The aim of this study is to evaluate the patients with TE whether they had COVID-19 or not before the onset of their hair loss and to compare the demographic and clinical characteristics and laboratory parameters of those with and without a history of COVID-19.

Method: We conducted an observational cohort study of TE patients. The diagnosis of TE depended on anamnesis and physical examination of the patients. Also, hair pull test was performed. Demographic data and the results of COVID-19 real-time polymerase chain reaction (RT-PCR) were recorded from the electronic medical records.

Results: Totally, 181 patients with TE were included in the study. Sixty-four of patients (35.4%) had been diagnosed with COVID-19 before the hair loss started. The median duration of development of hair loss was 2 months (range 1–11 months, IQR 3) after COVID-19 diagnosis. In this group, 87.5% of patients ($n = 56$) had acute TE and 12.5% of patients ($n = 8$) had chronic TE. The rate of acute TE and the use of vitamin supplements were ignificantly higher ($p < 0.001$ and $p = 0.027$, respectively) and the monocyte count in peripheral blood was lower ($p = 0.041$) in the group diagnosed with COVID-19.

Discussion and Conclusion: It was stated that monocytes and macrophages infected by SARS-CoV-2 can produce pro-inflammatory cytokines that play a crucial role in the development of COVID-19-related complications. Also, it was suggested that the number of monocytes tends to be lower in the late recovery stage. The lower monocyte count in patients with a history of COVID-19 in our study may be related to evaluating the patients in the late period of recovery and the migration of circulating monocytes to hair follicles. The history of COVID-19 must be questioned in patients with TE. It should be kept in mind that hair loss that develops after COVID-19 may be presented as chronic TE form too. The exact mechanisms of hair loss induced by COVID-19 are not fully explained; the roles of monocytes on the hair follicles may be one of the responsible mechanisms.

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), the cause of COVID-19 infection, has been associated with variable cutaneous findings including maculopapular, vesicular, urticarial rashes, and vascular lesions such as acro-ischemia, purpura, and livedo[1] At the same time, COVID-19 has previously been linked to telogen effluvium (TE). There are some reports in the literature stating that the incidence of TE increased during the pandemic period compared to the pre-pandemic period.[2–4] In several reports, it has been stated that the average onset time of the hair shedding was 1–3 months after the diagnosis of COVID-19.[5–10]

Telogen effluvium is one of the most common causes of non-scarring hair loss that is characterized by diffuse hair shedding and manifests commonly 2–3 months after the triggering factor such as metabolic or nutritional alterations, febrile diseases, and physiological or emotional stress or medications.[11] The possible pathogenetic mechanisms of the development of TE after COVID-19 have been tried to be explained with damaged hair matrix cells by cytokine storm and psychosocial and physical stress resulting from the "stay at home" orders, drugs such as heparinoids and direct viral damage to the hair follicle.[6,7,9,10]

To the best of our knowledge, to date, there was no study comparing the characteristics of the patients with TE depending on their previous COVID-19 status. The aim of this study was to evaluate the status of COVID-19 before the onset of hair loss in patients with TE and to evaluate clinical and laboratory differences between these two patient groups (patients with and without previous COVID-19 infection). The secondary objective was to investigate the possible pathogenetic mechanisms of post COVID-19 hair loss.

2 | MATERIALS AND METHODS

This descriptive, observational cohort study included patients with TE aged 18 years or older during the period between June 2021 and November 2021 in our dermatology outpatient clinics.

Demographic data of patients including age, gender, disease duration, presence of other systemic diseases, history of surgery, and/or delivery, using vitamin supplements including Vitamin C, Vitamin D, zinc, and multivitamins were noted. Results of COVID-19 real-time polymerase chain reaction (RT-PCR) test, hospitalization status and therapeutic agents used for COVID-19, and history of a close contact to a patient with confirmed COVID-19 infection were recorded according to statements of the patients and checked from e-Pulse (our National Personal Health Record System).

The diagnosis of TE depended on typical history like excessive hair shedding and physical examination findings as diffuse or bitemporal thinning. Hair pull test was performed on frontal, occipital, and both parietotemporal regions on the scalp by grasping about 50–60 hair between the thumb and index finger. Hair pull test was considered positive if more than 10% of pulled hair away. If the disease duration was less than 6 months, it was accepted as acute TE and if the disease duration exceeds 6 months, it was accepted as chronic TE. After the diagnosis of TE was made, laboratory examination including complete blood count, thyroid function tests, total iron-binding capacity, saturated/unsaturated iron-binding capacity, ferritin level, folate level, and Vitamin B12 level was performed. The NLR (neutrophil to lymphocyte ratio) value was measured by dividing the neutrophil count by lymphocyte count. The dNLR (derived neutrophil to lymphocyte ratio) was calculated using the formula dNLR = neutrophil count / (leukocyte count-neutrophil count). The PLR (platelet to lymphocyte ratio) was determined as the platelet count divided by the lymphocyte count and the MLR (monocyte to lymphocyte ratio) was measured by dividing the monocyte count by lymphocyte count.

Individuals younger than 18 years of age, being pregnant, receiving chemotherapy, having concomitant androgenetic alopecia, and a history of hair loss before the diagnosis of COVID-19 were not included in the study.

The statistical analysis was carried out using IBM SPSS Statistics 28.0. Continuous data were given as mean ± standard deviation (SD) and median ± Interquartile Range [IQR]. Categorical data were given as percentage. Pearson chi-square and Pearson exact chi-square analyzes were performed in the analysis of the cross tables. Mann–Whitney or independent samples t-tests were used for quantitative variables. For statistical significance, $p < 0.05$ was accepted as the criterion.

Informed consent was obtained from all patients. The approval of the Institutional Review Board was received (IRB approval status [approval date and number: 20.05.2021/602.03.99]).

3 | RESULTS

A total of 181 patients with TE were included in the study. One hundred seventy-two (95%) of the cases were female and 9 (5%) were male. The median age was 27 years (IQR 16). The median disease duration was 4 months (IQR 10). According to the disease duration, 65.2% of patients ($n = 118$) had acute TE and 34.8% of patients ($n = 63$) had chronic TE. The hair pull test was positive in 119 patients (65.7%). When we evaluated the hair pull test positivity according to the scalp areas, the most frequently positive areas were the left parietotemporal region, right parietotemporal region, occipital region, and vertex, respectively. There were 35 patients (19.3%) who had taken vitamin supplements for at least 15 days. (Table 1). There

TABLE 1 Clinical and demographic features of the patients

Number of patients, n (%)	181 (100%)
Gender, n (%)	
Female	172 (95%)
Male	9 (5%)
Age (year), median (IQR)	27 (16)
Disease duration (month), median (IQR)	4 (10)
Acute TE, n (%)	118 (65.2%)
Chronic TE, n (%)	63 (34.2%)
Hair pull test	
Positive, n (%)	119 (65.7%)
Negative, n (%)	62 (34.3%)
Hair pull test positive scalp areas, n (%)	
Vertex	72 (39.8%)
Right parietotemporal	83 (45.9%)
Left parietotemporal	88 (48.6%)
Occipital	80 (44.2%)
Vitamin supplement using, n (%)	35 (19.3%)

Abbreviations: IQR, interquartile range; TE, telogen effluvium.

were seven patients who had surgery history including rhinoplasty, appendectomy, and C/S before hair shedding. The median duration was 6 months (IQR 3) between the surgery and the onset of hair loss. Also, there were 11 patients who had a history of giving birth and the median duration was 7 months (IQR 7) between the delivery and onset of hair loss. The most common comorbid diseases were hypertension, hypothyroid, and diabetes mellitus.

Sixty-four of patients (35.4%) had been diagnosed with COVID-19 confirmed by RT-PCR test before the hair loss started. The median duration of development of hair loss was 2 months (range 1–11 months, IQR 3) after COVID-19 diagnosis. About 87.5% of patients (n = 56) had acute TE. There were eight patients with chronic TE. The clinical characteristics of these chronic TE patients are demonstrated in Table 2.

Hair pull test positivity was 64.1% in patients with previous COVID-19 infection. Eight of the patients (12.5%) required hospitalization for COVID-19 (Three of them required intensive care unit hospitalization). About 25% (n = 16) of the patients in this group did not use any medication for COVID-19. Favipiravir was the most common drug used for infection during the disease (n = 45, 70.3%). The other medications were hydroxychloroquine (n = 2, 3.1%), enoxaparin (n = 9, 14.1%), and plasmapheresis (n = 2, 3.1%). Also, RT-PCR tests were negative in 12 of 15 patients who had a history of close contact with a confirmed COVID-19 person and 3 of them had no PCR test. When we compared the groups that were diagnosed with COVID-19 before hair loss started and the group not diagnosed, in terms of demographic and clinical characteristics, there were no statistical differences between the groups about the gender, age, hair pull test positivity, hair pull test positive areas, having surgery, delivery, and/or comorbid disease history. The rate of acute telogen effluvium and the use of vitamin supplements were significantly higher

in the group diagnosed with COVID-19 (p < 0.001 and p = 0.027, respectively) (Table 3).

When we compared the laboratory parameters between the two groups, there was no statistically significant difference in the thyroid function tests, total iron-binding capacity, saturated/unsaturated iron-binding capacity, ferritin level, folate level, and Vitamin B12 level, and these parameters were in normal limits. In terms of complete blood count parameters, there was no statistical difference in hemoglobin, hematocrit, white blood cell and platelet counts, MCV, RDW, MPV, and PCT values between the groups. However, the median monocyte count was 0.41 ($\times 10^3/\mu l$) (IQR 0.18) in the group of patients with previous COVID-19 infection and 0.43($\times 10^3/\mu l$) (IQR 0.16) in other group and this difference was statistically significant (p = 0.041). NLR, dNLR, and MLR were lower and PLR was higher in the group of patients with previous COVID-19 infection, but these differences were not statistically different (Table 4).

4 | DISCUSSION

Telogen effluvium is a non-scarring alopecic condition that often occurs 2–3 months after the triggering event including infections, emotional stress, and medications. COVID-19 is an infectious febrile disease that is related to physiological and psychosocial stress and using some medications and all of them may be a potential causative reason for TE following COVID-19. In a study, it was reported that the incidence of TE increased from 0.5% to 2.3% 3 months after the COVID-19 pandemic was declared.[2] In another study, it was stated that the incidence of TE increased from 0.4% to 2.7% approximately 2 months after the declaration of a pandemic when compared to the corresponding month of the previous year.[3] On the other hand, the frequency of TE in individuals with diagnosed COVID-19 and recovered was also evaluated. In a study, TE was found to be 36.7% in post COVID-19 individuals.[10] In another study, it was reported that 24% of patients recovered from COVID-19 had alopecia as a late-onset symptom without specifying the subtype[12] As well, the frequency of TE was found to be higher with 66.3% in patients with a history of COVID-19 who were evaluated in specialized hair clinics.[13] To the best of our knowledge, there is no study in the literature evaluating the status of having COVID-19 prior to their complaints in patients diagnosed with TE. In our study, we found that more than a third of the TE patients (35.4%) were diagnosed with COVID-19 before the hair loss onset. Therefore, we would like to emphasize that it is important to question the history of COVID-19 in patients who present with hair loss and are evaluated as TE.

In the reports evaluating the hair loss after the diagnosis of COVID-19, the average onset time was stated as 1–3 months.[5–10] The median onset time of TE was 2 months after the COVID-19 diagnosis in our study consistent with the literature. When we grouped the patients according to the duration of the disease, acute TE was 87.5% in patients diagnosed with COVID-19, and the rate of acute TE was significantly higher than those without a history of COVID-19. Although postinfectious TE is traditionally categorized as acute TE,

TABLE 2 The clinical characteristics of patients with chronic TE after COVID-19

Patient no	Sex	Age (year)	Symptom duration (month)	Time after COVID-19 to presentation of hair loss (month)	Treatment for COVID-19	Hospitalized for COVID-19	Hair pull test	Medical history
1	Female	42	7	5	Favipiravir, enoxaparin	Yes	Positive (bilateral parietotemporal, occipital)	Diabetes mellitus
2	Female	28	7	1	Favipiravir	No	Positive (vertex, (left parietotemporal)	-
3	Female	25	10	1	Favipiravir	No	Negative	-
4	Female	36	8	2	Favipiravir, enoxaparin	No	Positive (vertex, occipital)	-
5	Female	59	9	2	Favipiravir	No	Positive (left parietotemporal)	-
6	Female	44	9	2	Favipiravir	No	Negative	-
7	Female	18	10	2	-	No	Positive (bilateral parietotemporal)	-
8	Female	19	11	1	-	No	Negative	-

in our study, there were eight patients (12.5%) who had chronic TE in the group with a history of COVID-19. These patients were similar to the other patients in terms of clinical features such as the median duration of disease onset after the COVID-19 diagnosis, hair pull positivity rate, and age. Only one patient with a history of diabetes mellitus required hospitalization for COVID-19. The studies in the literature that evaluated the TE after diagnosed with COVID-19, generally included patients with acute TE or did not evaluate whether patients developed chronic TE.[5,6,14] In order to determine the factors that play a role in the chronicity of TE after COVID-19, studies that require long-term follow-up with more patients are needed.

In our study, 95% of all patients were women, and this rate was similar in individuals who had a history of COVID-19 (92.1%). In studies in the literature, the rate of female sex in patients with TE with a history of COVID-19 has been reported between 77.9% and 92.3% similar to our study.[5–7,9,10,13,15] This might be explained by the fact that female patients notice hair shedding more easily due to their hair length and need to consult a physician more frequently because of taking hair loss more seriously than men.[11]

The use of vitamin supplements was significantly higher in the group with a history of COVID-19 in our study. This is an expected result because of a few reasons. First of all, these products are available over-the-counter medication in our country. The other explanation is that the vitamin or mineral supplementation may have a theoretical role in the prevention or treatment of COVID-19. Because of their potential to influence immune response and antioxidant capacity, they have been hypothesized to be useful for the prevention or treatment of COVID-19.[16,17]

Several pathogenetic mechanisms have been suggested to explain the development of TE after COVID-19. The cytokine storm is the most likely explanation that pro-inflammatory cytokines such as IL-6 (interleukin-6), IL-1β, TNF-α (tumor necrosis factor-alpha), and IFN-γ (interferon-gamma) may be responsible for inducing the catagen phase and damaging the hair matrix cells.[5,18] The inhibition of the hair growth by metalloproteinases 1 and 3 and IL-1β that showed high levels in COVID-19 may be another possible explanation.[6,19] It was hypothesized that SARS-Cov-2 may cause direct viral damage to the hair follicle via antibody-dependent enhancement phenomenon that an entry mechanism has been documented in coronaviruses.[6,20] In addition to these, the microthrombi formation due to the activation of the coagulation cascade and decreased concentration of anticoagulant proteins may occlude hair follicle blood supply and result in cell death.[7,10] In our study, we found that the monocyte count was statistically lower in patients with COVID-19 history. When we look at the relationship between monocytes and COVID-19, it was stated that monocytes and macrophages infected by SARS-CoV-2 can produce pro-inflammatory cytokines and chemokines resulting in the local tissue inflammation that plays a crucial role in the development of COVID-19-related complications.[21] It was shown that monocytes activate the extrinsic coagulation pathway and induce the appearance of thrombi. These results, for which monocytes are responsible, suggest that they are cell groups that play a fundamental

TABLE 3 Comparison of clinical and demographic features of patients with and without previous COVID-19 infection

	Diagnosed with COVID–19 (n = 64)	Not diagnosed with COVID–19 (n = 117)	p
Age (year), median (IQR)	30 (22)	25 (14)	0.058
Sex (female, n, %)	59 (92.1%)	113 (96.5%)	0.194
Disease duration (month), median (IQR)	2 (3)	6 (9)	<0.001
Acute TE (n, %)	56 (87.5%)	62 (53%)	<0.001
Hair pull test positivity (n, %)	41 (64.1%)	78 (66.7%)	0.724
Hair pull positive scalp areas (n, %)			
Vertex	24 (37.5%)	48 (41%)	0.643
Right parietotemporal	27 (42.2%)	56 (47.9%)	0.464
Left parietotemporal	31 (48.4%)	57 (48.7%)	0.971
Occipital	26 (40.6%)	54 (46.2%)	0.474
Vitamin supplement using (n, %)	18 (28.1%)	17 (14.5%)	0.027

Abbreviations: IQR, interquartile range; TE, telogen effluvium.

TABLE 4 Comparison of laboratory parameters of patients diagnosed with COVID-19 and not diagnosed

	Diagnosed with COVID–19	Not diagnosed with COVID–19	p
Hemoglobin(g/dl) $\pm$ SD	13.43 $\pm$ 1.24	13.42 $\pm$ 1.21	0.968
White blood cell count($\times 10^3$/μl)	6.81 (IQR 2.69)	7.45 (IQR 2.19)	0.103
Monocyte count($\times 10^3$/μl)	0.41 (IQR 0.18)	0.43 (IQR 0.16)	0.041
Mean platelet count($\times 10^3$/μl) $\pm$ SD	275.47 $\pm$ 6.95	272.50 $\pm$ 6.25	0.765
NLR	1.71 (IQR 0.87)	1.80 (IQR 1.1)	0.204
dNLR	1.42 (IQR 0.59)	1.48 (0.68)	0.285
MLR	0.18 (IQR 0.08)	0.19 (IQR 0.07)	0.076
PLR	117.2 (IQR 52.9)	112.8 (IQR 44.6)	0.790
Ferritin(μg/L)	16.85 (IQR 22.28)	14.65 (IQR 15.63)	0.128

Abbreviations: dNLR, derived neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.

role in the development of post-COVID-19 TE. Also, it has been observed that the number of monocytes varies according to the stages of COVID-19 and tends to be lower in the late recovery stage than in the early recovery stage.[22] In another study, it was shown that the severity of COVID-19 was found to be relevant to the tendency of lower percentages of monocytes.[23] Likewise, in a study that evaluated the profile of immune cells in the circulation and lungs of patients with COVID-19 and healthy controls, the authors found a substantial decrease in the circulating monocytes of COVID-19 patients and suggested that it may be associated with monocyte trafficking to the lungs.[24] The lower monocyte count in patients with a history of COVID-19 in our study may be related to the fact that the patients were evaluated months after the disease, in the late period of recovery, and migration of circulating monocytes to hair follicles. Whether there is a difference in initial monocyte levels between those with and without TE who have COVID-19 history may be the subject of a separate study.

Biomarkers derived from peripheral blood such as NLR, dNLR, PLR, and MLR have been investigated in COVID-19 patients in several studies. In a study, elevated NLR was found an independent prognostic biomarker for COVID-19 severity.[25] In another study, it was calculated that PLR and NLR were statistically higher in patients with positive SARS-Cov-2 test result than those with negative test result.[26] In our study, PLR was higher in patients with a history of COVID-19, but this difference was not statistically different. Similarly, no difference was found between the two groups in the NLR, dNLR, and MLR ratios.

The medications used for the treatment of COVID-19 may be a potential role in the development of TE after COVID-19. The role of anticoagulants including enoxaparin in the development of TE has been mentioned in the literature. It was described that TE started 3 weeks after drug administration.[27] To the best of our knowledge, favipiravir- and/or hydroxychloroquine-induced telogen effluvium has not been reported to date, but it cannot be excluded whether they cause TE. In our study, since the median onset time of TE was 2 months and the number of patients using enoxaparin was low, no relationship could be established between drug use and the development of TE.

There are several limitations in our study. We did not use trichoscopy and trichogram techniques to diagnose TE. We did not maintain a long-term follow-up of those with TE after COVID-19 in order to evaluate their chronicity. Since the majority of individuals in this group recovered by receiving outpatient treatment for COVID-19 infection, we could not evaluate whether there was a difference between disease severity and clinical features of TE. COVID-19 has an effect on the psychosocial condition of patients and we did not evaluate whether was a difference between the two groups in terms of anxiety and depression levels of the patients.[28]

As a conclusion, in our study, we found a history of COVID-19 in 34% of patients diagnosed with TE in our outpatient clinic. For this reason, the history of COVID-19 must be questioned in patients who have the complaint of hair loss and been diagnosed with TE. Hair loss that develops after COVID-19 may not be only in acute TE form; therefore, it is necessary to follow up the patients. Although the exact mechanisms of hair loss induced by COVID-19 are not well known, the effects of monocytes on the hair follicle may be one of the responsible mechanisms in addition to the data in the literature.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Sema Koç Yıldırım: Conceptualization; visualization; data curation and writing original draft. Ece Erbağcı and Neslihan Demirel Öğüt: Data curation and editing.

ETHICAL APPROVAL

Informed consent was obtained from all patients. The approval of the Institutional Review Board was received (IRB approval status [approval date and number: 20.05.2021/602.03.99]).

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Sema Koç Yıldırım https://orcid.org/0000-0002-0633-1770
Ece Erbağcı https://orcid.org/0000-0002-2887-0492
Neslihan Demirel Öğüt https://orcid.org/0000-0001-5051-5481

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