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Review Article

Acute telogen effluvium related to COVID-19 infection: A review

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Abstract

Background Since being declared a pandemic, Coronavirus Disease 19 (COVID-19) has spread worldwide and causes various manifestations, including hair symptoms. Infection with COVID-19 produces inflammation and stress, which results in dermatological symptoms affecting the skin and hair. The most common hair loss-related finding in COVID-19 instances is Telogen Effluvium (TE), which is characterized by widespread non-scarring hair loss. The hair shedding that occurs usually happens two to three months after infection. In this article, we review and summarize how hair loss was induced in COVID-19 infections, how TE and COVID-19 severity is associated, as well as the duration and onset of TE following COVID-19 infections.

Methods A literature search through PubMed was performed and nine studies were found. Studies included case reports and case series published from 2020 to 2021.

Results From the nine studies reviewed, we found more than 50% of females suffered from post-COVID TE, with an age range of 20-76 years old and a mean age of 42.89 years old. The average number of days to TE onset was ±63 days after COVID-19 infection. TE was discovered in patients with mild to moderate COVID-19. Several studies have found that Caucasians are more likely to suffer from TE compared to other racial groups. The comorbidities in most of the patients included vitamin D deficiency, anemia, hypothyroidism, and type 2 diabetes mellitus.

Conclusion Various factors influence post-COVID TE, including age, time of onset, gender, severity of COVID-19 infection, and pre-existing comorbidities (vitamin D deficiency, anemia, hypothyroidism, and type 2 diabetes mellitus).

Key words
Telogen effluvium, hair loss, COVID-19, SARS-COV-2.

Introduction

Telogen effluvium (TE) is one of the most common causes for hair loss, where a premature shift from the anagen (growing) phase into the catagen (involuting) and telogen (terminal) phases occur.[1] TE is defined as a noninflammatory disease characterized by a non-scarring form of diffuse hair loss.[1] TE might be caused by stress, medications, childbirth, metabolic disorders, surgical interventions, inflammation, and diet.[2,3] TE can be classified as acute and chronic.[3]

Coronavirus disease of 2019 (abbreviated COVID-19) has spread rapidly around the world, escalating into a pandemic. However, as the pandemic spread, it became evident that this virus exhibited several specific features which resulted in widespread disease processes, not only in the lungs but also in extra pulmonary sites, such as TE of the hair.[4] In previous reports, TE can occur within 2 to 12 weeks after COVID-19 infection.[5] This review aims to summarize the available literature on TE and its

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relationship with COVID-19 infections.

Methods

This review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was performed in the PubMed database for studies published within the years 2020 and 2021. The keywords used in the search included the following: "Telogen Effluvium in COVID-19" and "Hair loss in COVID-19". Our inclusion criterion was studies on TE in COVID-19 infection. We collected data on countries of origin, prevalence of hair loss in COVID-19 patients, baseline characteristics of study subjects (age, gender, ethnicity, duration of hair loss, severity of infection, laboratory findings, comorbidities), and treatment. We excluded studies that do not associate TE with COVID-19 and case reports or case series with a small number of patients (less than 5 patients).

Discussion

We reviewed nine studies to describe the characteristics of TE related to COVID-19, such as age, gender, ethnicity, severity of COVID-19 infection, laboratory findings, comorbidities, duration of hair loss, and treatment given for COVID-19 **(Table 1)**.

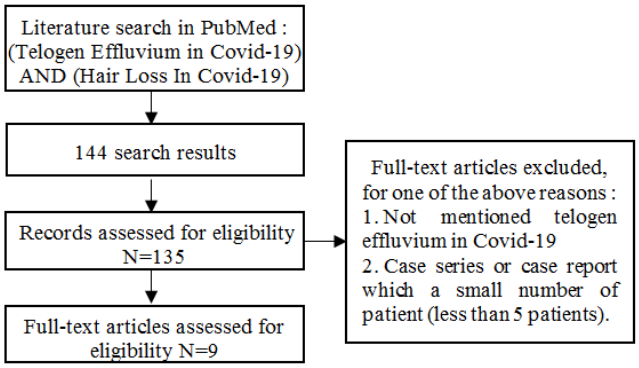

Figure 1 Prisma flow diagram describing the search process.

In the nine studies reviewed in this article, we found a mean age of 42.89 years, with a range of 20-76 years. This finding is similar to Fatani *et al*.'s study that documented in their retrospective review that TE was found in not only 21-40 year olds but also affected females aged 30-60 years old. Based on the studies reviewed, more females are affected with TE compared to men. Approximately more than 60% of the subjects in all studies were female.[6] The proposed reasons are as follows: (1) females typically have long hair and can easily recognize hair shedding; (2) females are inclined to seek medical help more often; (3) females are more susceptible to stress.[7]

Our review found that in 16 patients with TE, 7 were identified as White/Caucasian, 7 were Black, 1 was Middle Eastern, and 1 was Asian. Maymone *et al*. found that the hair density of Caucasians was highest than other subgroups like Black, Asian, and Hispanic/ Latin. Average hair density depended on hair fibers and determined the hair cycle; Caucasian population tend to have shorter anagen phase with aging and longer telogen phase, making them more susceptible to hair loss.[6]

African hair had a slower rate of growth compared to Asian hair. After around half of the hair has fallen out, people start to notice hair loss. Shed hair fibers in Caucasian and Asian races are full-length hair shafts with a telogen club, whereas shed African hair shafts are generally shorter, with no proximal club and signs of longitudinal fissures, implying that hair is lost through breakage. However, further clinical and experimental studies with a larger number of participants are required.[6]

Onset and duration of COVID-19 infection-induced TE

Based on 9 studies and 922 patients that we

reviewed, the reported mean time of onset was ±63 days after COVID-19 infection. A similar study was conducted by Saeed *et al*. who reported that the onset of COVID-19-related TE was between 1 to 2 months after COVID-19 infection.[8] Wei *et al*. reported a total of 28 patients with TE, with onset of hair shedding averaging on 73 days after the first symptoms of COVID-19.[9] According to Asghar *et al*., increased stress response can provoke acute TE, including fever and inflammation, and TE might occur approximately two to three months after exposure.[10] Hair follicles can continue to grow for 2-6 years, then begin to retreat in the involuting (catagen) phase. Hair follicles stay in the catagen phase for around 3 weeks. Hair follicles are inactive during the telogen phase, which lasts about three months on average.[11] Post-febrile TE in COVID-19 infection may be caused by high temperature, which may also change the normal hair cycle. The cytokines released due to fever prematurely push the follicles to enter the catagen phase and subsequently the telogen phase.

Mechanisms of COVID-19 infection-induced TE and association with COVID-19 clinical severity

Five of the nine studies presented evidence on TE related to the severity of COVID-19 infection. The majority of the studies showed patients with mild to severe COVID-19 infections. Olds *et al.* showed in moderate to severe COVID-19 infection, acute TE could be induced by the massive release of pro-inflammatory cytokines as an aftermath of viral infections, and in severe COVID-19 infections, strong antiviral responses are induced. Interferons, a molecule that has been reported to induce TE, also play a big role.[5]

This is consistent with Del Valle *et al.*'s study which reported high serum levels of IL-6, IL-8, and TNF-α in patients admitted to the hospital with COVID-19. These were subsequently demonstrated to be strong and independent predictors of patient survival. Even after adjusting for disease severity, inflammatory markers, vitals, demographics, hypoxia, and comorbidities, they found serum levels of IL-6 and TNF-α are independent and significant predictors of disease severity and death.[12]

In COVID-19, interleukin (IL)-6, a pro-inflammatory cytokine, plays a crucial role. When hair follicles are exposed to high amounts of IL-6, local inflammation and breach of immune privilege ensues, elongating the catagen phase. Interleukin-4, which is reported to be associated with COVID-19 in elderly patients, have been demonstrated to influence keratinocyte death in hair follicles. Moreover, direct viral damage to hair follicles is hypothesized to be the underlying mechanism of COVID-19-related TE, due to the early onset of TE after COVID-19 infection. SARS-CoV-2 is characterized by superficial spike glycoproteins, which bind angiotensin I-converting enzyme-2 on host cells, allowing for pathogen entry.[13]

A study by Rivetti *et al.* reported that the mechanism of mild COVID-19 infection was correlated with the brain-hair follicle axis.[14] The connection between a stressor as the precipitating factor in the slower rate of hair growth cycle has attested the existence of a brain–hair follicle axis. The release of certain neurotransmitters, neuropeptides, and hormones along the brain-hair follicle axis induce the changes in hair cycles and the shifts between anagen and telogen phases.

Predisposition Factors and Laboratory Findings

Fatani *et al*. reported that from the 279 patients of TE they observed, 20.8% had acute TE and

79.2% had chronic TE. The patients presented with hypothyroidism (21.1%) and diabetes mellitus (5.7%). Several abnormalities in laboratory work-ups were found in the patients; 94.9% had low hemoglobin, 90.2% had low hematocrit, 31% had low MCV, 99.6% had low MCH, and serum ferritin level at 70 ng/mL was found in 19.35% of patients with acute TE and in 80.5% of patients with chronic TE. These laboratory results may support the evidence that iron-deficiency anemia may be associated with TE.[15] Aligned with our study, Babaei *et al*. found similar comorbidities in the 526 patients included in their study, namely hypothyroidism (21%), diabetes (19.9%), iron deficiency anemia (13.8%) and vitamin D deficiency (24.3%).[7]

Grymowicz *et al*. reported delayed activation of the hair follicles in animal hypothyroidism. Triiodothyronine (T3) and thyroxine (T4) were known to cause increased melanogenesis in hair follicles and can affect important hair follicle functions, including prolongation of the anagen phase, stimulation of the hair matrix, keratinocyte proliferation and pigmentation, and changes to intracellular keratin expression.[16] In contrast, Ozuguz *et al*. reported no significant differences in thyroid function between patients with chronic TE and the control group.[17] Another study by Kakpovbia *et al*. reported that 167 patients with TE was found to have a low prevalence of hypo- or hyperthyroidism.[18]

Keratinocytes are skin cells which produce keratin, and their growth and differentiation can be stimulated by vitamin D, which binds to the nuclear vitamin D receptor (VDR). These receptors are found in the mesodermal dermal papilla cells in epidermal keratinocytes as well as in hair follicles. The expression of VDR in hair follicles is increased during late anagen and catagen phases, correlating with decreased proliferation and increased differentiation of the keratinocytes. Keratinocytes in the hair follicles of mice are immunoreactive for VDR. They show the most activity in the anagen stage. Patients with type II vitamin D-dependent rickets experience hair loss, and this shows how vitamin D can affect hair follicles. In type II vitamin D-dependent rickets, VDR gene mutations are found, which lead to resistance to vitamin D, patchy body hair, involving the scalp, and body alopecia.[19,20]

COVID-19 treatment-induced telogen effluvium

Numerous drugs can cause TE, including retinoids, oral contraceptive pills, androgens, antihypertensive agents such as beta-blockers, angiotensin-converting enzyme inhibitors, anticonvulsants, antidepressants, antithyroid, anticoagulants (heparin), and minoxidil.[21]

We found 3 out of the 9 studies that reported the use of enoxaparin as treatment of COVID-19. Severe COVID-19 infections are associated with disturbances of the coagulation cascade and a decrease in circulating anticoagulation factors. These mechanisms are possibly linked with microthrombi and occlusion in micro-vessels of the hair follicle. Hence, an increase of hair shedding occurs.[5]

Conclusion

In this review, we found that the most prevalent characteristics in patients experiencing post-COVID TE were female sex and aged 20-76 years old. Hair loss occurred within 2-3 months of COVID infection and most post-COVID TE cases were found in mild to moderate COVID-19 infections. Comorbidities found in patients with post-COVID TE include vitamin D deficiency, anemia, hypothyroidism, and type 2 diabetes mellitus. Healthcare providers should be aware of the association between TE and COVID-19 to be able to provide patients with relevant information.

Table 1 Characteristics of telogen effluvium.

Author *Year* *Country* *Number of Cases*	*Age (years)*	*Gender (Female) %*	*Races / Ethnicites*	*Onset / phase in Covid-19*	*Grading of Covid*	*Predispotition Factors.*	*Treatment during Covid.*
Babaei K, *et al.* 12 months in 2020. Iran 526	8 - 62 years old with a Mean age of 30.97 ± 9.592	77.9%	NR	Mean time 7.65±1.739 weeks After Covid infection	Moderate to severe Covid-19 36.7% (193 patient)	Vitamin D defiency (24.3%) Hypothryoidism (21%) Diabetes (19.9%) Iron Defiency Anemia (13.8%) Smoking (10.8%) Alcohol consumption (8.2%)	NR
Starace, *et al*. (from April 2020 to September 2020) Italy 45	Mean 45	83.1%	NR	the first month (after 4 weeks) after COVID-19 diagnosis	Mild COVID-19 57,1%. 24 cases TE+TR Moderate to Severe Covid-19 50% 80% (128 Patients)	NR	NR
Olds, *et al*. between February 2020 and September 2020 United States 10	28 to 62 years old with Mean 48.5	90%	Six of the patients were Black, one Middle Eastern, and three White.	the hair shedding began 50 days after the first symptom of COVID-19 infection	NR	NR	Azithromycin, Ceftriaxone, Hydroxychloroquine, Prednisone, Methylprednisolone
Rossi *et al*. Between August and November 2020 Italy 14	23-64 years old with Mean 47.57	78.5%	NR	Median 2 months	NR	Seborrheic Dermatitis Androgenetic Alopecia	Azithromycin, Ceftriaxone, Darunavir + cobicstat, Hydroxychloroquine, Levofloxacin Paracetamol, Pantoprazole, Tocilizumab
Aksoy, *et al*. February 2021 and April 2021. Turkey 57	Mean 48.8	women compared to men (42.3% vs. 6.2%)	NR	Average 53.76 (±23.772) days after COVID-19 RT-PCR positive	NR	Hypertension (40.4) Diabetes Melitus (26.2)	Favipiravir, Antibiotics, Enoxaparin, Corticosteroids, Parasetamol, Lopinavir, Acetylsalicylic acid, NSAID, Hydroxychloroquinone
Sharquie, K and Raed I. september 2020 to March 2021 Ireland 39	22 - 67 years with a mean and SD of 41.3±11.6	92.3% females	NR	2–3 months after COVID-19 infection	(61.53%) patients presented with moderate COVID-19	NR	-a multi-drug regimen according to the National Guidance for Clinical Management and Treatment of COVID-19 for the treatment of mild and moderate COVID-19 infection :

Author *Year* *Country* *Number of Cases*	*Age (years)*	*Gender (Female) %*	*Races / Ethnicites*	*Onset / phase in Covid-19*	*Grading of Covid*	*Predispotition Factors.*	*Treatment during Covid.*
	years						antiviral therapy (favipiravir tablet for mild disease, favipiravir tablet or lopinavir-ritonavir tablet for moderate infection) antibiotics (ceftriaxone injection, oral azithromycin, or oral levofoxacin), dexamethasone injection, anticoagulant (enoxaparin), supportive therapy (antipyretics, tonics suchas, zinc, selenium, and vitamins D and C), and oxygen
Mieczkowska, *et al*. NR USA 10	Mean 55	100%	Black 1, White 4	Mean 4.25 months.	6 reported mild symptoms, and 4 presented with severe disease requiring hospitalization.	Hypothyroidism (2), NASH cirrhosis (1), Obesity (2), PCOS (2), Hyperlipidemia (3), Emphysema (1), CKD Stage III (1), Breast cancer (1), Type 2 Diabetes Mellitus (3), Depression (1), Asthma (2), Osteoarthritis (1), Hypertension (1)	Azithromycin Doxycycline Ceftriaxone Hydroxychloroquine
Moreno, *et al*. March to August 2020 China 191 patients	Mean 47.4 years	150 female (78.5%)	NR	57.1 days	136 patients 971.2%) required ambulatory 40 patients (20.8%) required hospitalization 15 (7.8%) required admission to the intensive care unit	NR	Paracetamol: 75.4% (144) NSAIDs : 14.7% (28) Oral corticosteroids: 26.2% (50) Oral antibiotics: 42.9% (82) Lopinavir/ritonavir: 19.9% (38) Remdesivir: 5.2% (10) Tocilizumab: 13.54% (26) Enoxaparin: 50.5% (97)
Abrantes, TF, *et al*. United States, Brazil, and Spain 30 Patients	NR	21 patients (70%)	NR	Median 47.5 days	NR	26.7% of patients (5 men, 3 women) had a history of androgenetic alopecia.	NR

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