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Post-COVID Telogen Effluvium

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ABSTRACT Recently, the number of patients with acute telogen effluvium (ATE), among other forms of hair loss, has increased in comparison with previous years. The COVID-19 pandemic, taking place during this period, may be the cause of this phenomenon. The exact mechanisms by which this virus causes hair loss are not entirely understood; still, the most likely cause is an excessive release of proinflammatory cytokines during SARS-CoV-2 infection. This process can trigger the development of telogen effluvium (TE) by damaging hair matrix cells. Additionally, the psychosocial condition of patients recovering from COVID-19 will have deteriorated, contributing to hair loss. Based on data collected until now, post-COVID TE is expected to improve without any treatment. Although there is no specific treatment for post-COVID TE, eliminating psychophysical stress, managing systemic complications, and explaining the course of the condition to the patient will potentially improve and speed up the hair recovery process.

KEY WORDS: COVID-19, hair loss, telogen effluvium, pathophysiology, treatment

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus, a virus that belongs to the *Coronaviridae* family, firmly associated with severe acute respiratory syndrome (SARS) (1,2). It broke out in Wuhan, China, in December 2019, and on March 11, 2020, the WHO officially declared a COVID-19 pandemic (3). Many infected individuals are asymptomatic; however, some patients with COVID-19 develop a strong immune response that causes multiple organ injuries. The infection presents with flu-like symptoms in most symptomatic cases, such as fever, fatigue, and dry cough. In addition, headache, myalgia, nausea, and diarrhea may also occur in patients with COVID-19 (4,5).

In these patients, proinflammatory cytokines and chemokines, including interleukin (IL) -1, IL-2, IL-6, IL-8, IL-10, IL-17, IL-18, CXCL10, and CCL2 were significantly increased. Expression levels of some of these cytokines, such as IL-1, IL-6, IL-10, and IL-18, are associated with disease severity (5-8). Excessive production and release of proinflammatory cytokines and chemokines can cause severe organ damage in critical cases.

Some patients experience a wide range of health consequences that are present 12 or more weeks after the onset of COVID-19 and cannot attributed to an alternative diagnosis. These symptoms are termed post-COVID syndrome (9). Telogen effluvium (TE) has been recognized as the most common dermatological manifestation of post-COVID syndrome.

TELOGEN EFFLUVIUM

TE is excessive hair loss in the telogen phase of the hair cycle, first described by Kligman as an increased shedding of telogen hairs in a non-specific pattern, developing 3-4 months after the precipitating event (10). Alopecia only occurs when approximately 40% of hair falls out (10). TE can be considered when hair loss exceeds 100 hairs per day (11). This number varies considerably; the median is about 300 hairs but may exceptionally exceed as many as 1000 hairs (12). TE is characterized by diffuse, non-scarring hair loss within 2-3 months after stress (13). The precipitated event causes premature termination of the anagen phase and subsequent transition to the catagen and telogen phase, resulting in hair loss. TE is usually self-limiting; acute TE (ATE) typically resolves within six months, and if it lasts longer than that, it should be considered chronic TE (14,15). Although Kligman suggested the association between TE and febrile and chronic systemic diseases, major surgeries, emotional stress, and childbirth, he failed to find histological inflammatory signs that would prove these possible causal associations. However, he reported an increased proportion of telogen follicles (10). Sulzberger *et al.* described the specific symptom associated with TE, "hair pain", which was later called trichodynia. In addition, they described an unexplainable increase in diffuse hair loss in postpubertal women (16). Whiting suggested the chronic course of the disease and confirmed Kligman's histopathological findings (17).

A diagnosis of acute telogen effluvium can usually be established based on the patient history, physical examination, a hair pull test, and trichogram. Although the hair pull test is strongly positive in active TE, it is not an obligatory finding (18). Trichoscopy is characterized by a decrease in hair density and the occurrence of empty follicles. The entire scalp is affected. There are no variations in hair shaft diameter variation, and there are no peripheral halos like in androgenetic alopecia (19). In rare cases, a scalp biopsy may be required. Multiple scalp biopsies with horizontal sections are more accurate than a single biopsy (20). The anagen-telogen ratio in chronic TE is 8:1 (compared with 14:1 in the normal scalp). The total number of hairs and the ratio between the terminal and velus hairs (8:1) are the same in chronic TE and normal hair (21).

SARS-COV-2 INFECTION AS A PRECIPITATING FACTOR FOR ACUTE TELOGEN EFFLUVIUM

Hair loss was observed during the influenza pandemic (Spanish flu) that occurred from 1918 to 1920. It usually occurred 2 to 6 weeks after the onset of a high fever (22). In addition, an association of ATE with dengue fever, human immunodeficiency virus (HIV) infection, malaria, typhoid fever, pneumonia, scarlet fever, tuberculosis, and pertussis has been reported (23,24). Therefore, the occurrence of TE after COVID-19 should not have been surprising.

After the onset of the COVID-19 pandemic, some authors reported changes in the incidence of certain diseases in dermatology outpatient clinics compared with the pre-pandemic era. One of the diseases with an increased incidence in the era of the COVID-19 pandemic was TE. Kutlu *et al.* reported that the COVID-19 pandemic led to a 5.51 times increased percentage of TE presenting to outpatient clinics in Turkey from May 2019 to May 2020 compared with the same period in the previous year (25). Additionally, a retrospective analysis performed by Cline *et al.* showed that the incidence of TE in the investigated dermatology departments increased by >400% in July and August 2020 compared with February 2020 (2.3% vs. 0.5%) (26).

One of the first publications that recorded a relationship between COVID-19 and hair fall was a large-scale study (538 cases) performed in Wuhan, China investigating clinical sequelae of COVID-19. In 28.6% of patients, alopecia was detected as a consequence of COVID-19 (27).

Rizzeto *et al.* were the first to report a case series describing TE in patients post severe COVID-19 (28). In these cases, the time interval between the onset

Table 1. Studies reporting the prevalence of post-COVID telogen effluvium (TE)

Authors	Country	Year	Number of participants (patients who underwent COVID-19)	Telogen effluvium prevalence N (%)
Olds H *et al.* (35)	USA	2020	552	10 (1.8%)
Turkmen D *et al.* (36)	Turkey	2020	563	157 (27.9%)
Miyazato Y *et al.* (33)	Japan	2020	58	14 (24.1%)
Monari *et al.* (37)	Italy	2020	96	30 (31.3%)

of hair shedding and COVID-19 infection was 75, 60, and 36 days, respectively, for the three described cases (28). Additionally, an observational cross-sectional study was conducted by Sharquir *et al.* from September 2020 to March 2021, wherein 39 patients with hair loss after COVID-19 infection were reported (29). The effluvium occurred after mild to moderate COVID-19 disease. All affected patients experienced hair falling out in large clumps 2-3 months after COVID-19 infection. Their dermatologic examination showed a strongly positive hair pull test with moderate-to-severe reduced hair density. In 43.58% of patients, the hair loss pattern was diffuse, frontovertical in 30.76%, and in bitemporo-frontal 5.12%. No alopecic patches, erythema, or scaling were observed (29). Babaei *et al.* conducted a cross-sectional study that included 526 patients with documented telogen effluvium after COVID-19 infection (30). Androgenetic alopecia (78.2%), vitamin D deficiency (24.3%), and hypothyroidism (21%) were the most common associated diseases. Although both hypothyroidism and vitamin D deficiency may cause telogen effluvium (31), in reported patients, these conditions could exacerbate or make hair loss chronic in association with COVID-19 infection (30). In younger patients, alopecia occurred significantly earlier; the earlier onset was also noted in women, patients with hypothyroidism, and severe coronavirus infection. A higher degree of disease severity has been observed in men, the elderly, and patients with androgenic alopecia (30). Moreno-Arrones *et al.* conducted a prospective, multicentric study from March to August 2020, which enrolled 214 participants with ATE. Among them, 191 patients had a confirmed diagnosis of prior SARS-CoV-2 infection (32). Most participants were women (78.5%); 86.4% of all participants had a fever and only 13.6% were asymptomatic. ATE was active in 72.8% of cases four weeks after the diagnosis (32). The mean number of days between COVID-19 diagnosis and significant hair shedding was 51.1 (32). Since 13.6% of patients had an asymptomatic SARS-CoV-2 infection before ATE, the authors suggested that every patient suffering from ATE during the COVID-19 pandemic should be considered for previous SARS-CoV-2 infection (32). Miyazato *et al.* conducted one-to-one structured individual telephone interviews with the patients during the recovery period of COVID-19 disease (33). The results showed that 24.1% of patients with COVID-19 reported alopecia 58.6 days after symptom onset and that the mean duration of alopecia was 76.4 days (33). None of the participants reported late-onset symptoms other than alopecia (33). Rossi *et al.* reported 14 cases of new-onset TE occurring between 1 and 3 months after SARS-CiV-2 infection (34). While trichoscopy features and trichogram examination showed no variation from classic TE, time to onset was shorter in COVID-19 TE. The authors hypothesized that direct viral damage to hair follicles in the setting of SARS-CoV-2 infection might cause an early onset of COVID-19 TE (34).

The prevalence of TE among patients with COVID-19 has not been sufficiently studied and varies between 1.8% and 31.3% (Table 1).

The wide range of post-COVID TE prevalence may be due to various factors such as the methodology, sample size, previous hair disorders, and genetics.

COEXISTENCE OF ANDROGENETIC ALOPECIA AND POST-COVID TELOGEN EFFLUVIUM

The association between androgenetic alopecia (AGA) and COVID-19 has been most often discussed in terms of a possible association between AGA and the severity of COVID-19. Namely, Wambier *et al.* conducted a study that included 175 individuals (122 men and 53 women) with confirmed COVID-19 infection (38). Overall, 67% of the patients presented with clinically relevant AGA, which was also the most common type of concurrent alopecia in these patients. Interestingly, the coexistence of TE and AGA showed an overall poor prognosis with regard to the improvement of hair density (38).

The coexistence of AGA and post-COVID TE was observed in the study performed by Abrantes *et al.* (39). They evaluated the onset and duration of acute post-COVID TE in 30 patients, among whom 26.7% had a history of AGA (39). Acute TE occurred at a median of 45 days after a positive reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2, which indicated that post-COVID TE appeared sooner compared with TE triggered by other factors (39). Resolution of TE in most of their cases was observed after less than two months (39), while typical TE takes three to six months to cease (40). The authors concluded that a severe post-COVID TE with a shorter duration could unmask preexisting AGA and reduce hair density (39). Trüeb *et al.* similarly observed early onset effluvium in 3 cases of confirmed COVID-19 infection with preexisting AGA (41).

COEXISTENCE OF TRYCHODINIA AND POST-COVID TELOGEN EFFLUVIUM

In earlier studies, the association between telogen effluvium and trichodynia was reported in cases not associated with COVID-19 (42). In addition, it has been shown that trichodynia is related to the intensity of hair shedding (42).

DiLandro *et al.* observed 39 patients presenting with post-COVID TE, including seven patients who also had severe trichodynia (43). Both hair loss and trichodynia were resolved in 2 to 4 months. The authors discussed whether trichodynia could develop via similar neuropathologic mechanisms like the one leading to SARS-CoV-2-induced anosmia and ageusia (43). In a recent study done by Starace *et al.,* data from 128 patients with a history of COVID-19 infection were collected (44). TE was observed in 66.3% of the patients, whereas 58.4% of patients had trichodynia (44). TE associated with trichodynia was found in 42.4% of the patients, while anosmia and ageusia were observed in 66.1% of cases (44). Trichodynia is not specific to TE and may be associated with androgenetic alopecia and psychiatric disorders, including depression and anxiety (45). Although the pathophysiology of trichodynia is not completely clear, it has been suggested that substance P, a stress-related neuronal peptide released by the peripheral nerve endings involved in nociception and the neuroinflammatory pathways, may be related to the condition (46).

PATHOPHYSIOLOGY OF POST-COVID TELOGEN EFFLUVIUM: CURRENT HYPOTHESES

SARS-CoV-2 is characterized by superficial spike (S) glycoproteins that allow pathogen entry by binding to a host cell (13). Hoffmann *et al.* showed that SARS-CoV-2 used transmembrane protease serine 2 (TMPRSS2) for S protein uptake and the angiotensin-converting SARS-CoV receptor (ACE2) for entrance (47). Therefore, all cells carrying the ACE2 receptor, including the cells within the skin, are potential targets for SARS-CoV-2.

Cutaneous manifestations of COVID-19, such as livedoid vasculopathy, urticaria, pernio, and chickenpox-like rash, may occur due to either a direct cytopathogenic effect on cells, such as keratinocytes, or the excessed release of cytokines, including tumor necrosis factor (TNF)-α, IL-1b, IL- 6, and interferon (IFN) types 1 and 2 (48).

A cytokine storm can trigger the development of TE by damaging matrix cells. It has been shown that matrix cells express the IL-6 receptor in cultured hair follicles, while IL-6 inhibits their proliferation and hair shaft elongation (49). Furthermore, it has also been confirmed that high levels of IL-4, which are typical for COVID-19 in the elderly, also determine keratinocyte apoptosis in hair follicles (50). Recombinant IFN alpha-2b therapy has also been reported to induce TE (51).

Rossi *et al.* hypothesized that SARS-CoV-2 may directly affect the hair follicles via antibody-dependent enhancement (ADE) (34). The AED mechanism is due to non-neutralizing virus-specific antibodies (Nab) present in patients with SARS-CoV-2, which interact with Fcy and/or complement receptors expressed by hair follicle dermal papilla cells (52). The ADE phenomenon has also been documented in dengue virus infection and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) (53).

Since TE is a disease that is mainly induced by stressful conditions, increased psychosocial stress due to COVID-19 may exacerbate it (54-57). These psychological reactions, such as anger, irritability, and anxiety, cause the release of specific neurotransmitters, neuropeptides, and hormones that promote changes in hair growth, stimulating the transition of hair from the anagen to the telogen phase (58).

Potential role of enoxaparin in post-COVID telogen effluvium development

Enoxaparin is one of the commonly prescribed medications in patients with COVID-19 (59). Previous studies have reported the association between anticoagulant treatment and hair loss (60,61). Watras *et al.* described patients without a history of COVID-19 who developed TE 3 weeks after enoxaparin administration (60). Subsequently, when investigating post-COVID TE, Sharkie *et al.* pointed out that their patients who developed post-COVID TE and had been previously treated with enoxaparin, developed hair loss 2-3 months after COVID-19 infection (29). Furthermore, the mean dose of enoxaparin used in their study (75 IU/kg once daily as a prophylactic agent and 75 IU/kg twice daily as a therapeutic agent) was lower than in the previous study by Waldas *et al.* (100 IU/kg twice daily) (29,60). Therefore, the authors concluded that enoxaparin was a less likely cause of ATE than COVID-19 infection (29).

Additional studies of hair follicle tissue are required in order to further elucidate the definitive mechanism of TE after COVID-19 infection.

CURRENT TREATMENT OPTIONS

There is no specific treatment for telogen effluvium (61). However, different therapeutic options are available to improve ATE, including minoxidil, steroids, vitamins, platelet-rich plasma injections, and iron supplements (62). Post-COVID TE treatment is based on eliminating primary psychophysical stress and managing systemic complications (63).

The most important aspect in the management of TE is counseling the patient about the natural progression of the condition and the relationship

between triggers and timing of hair loss (31,62). Attempts should be made to identify the specific cause, and once identified, they have to be corrected (62). Hair shedding takes 3-6 months to cease, after which regrowth can be observed 3-6 months after removal of the trigger, but cosmetically significant regrowth can take 12-18 months (64,65). We know that stress is one of the major contributing factors to telogen effluvium, and there is no specific therapeutic intervention that could prevent stress-induced premature onset of catagen (40,66). Substitution therapy can be initiated for catagen-promoting deficiencies (such as iron, zinc, estradiol, and proteins) (64,67).

CONCLUSION

COVID-19 infection is now known to be a common cause of acute telogen effluvium. We are still learning about post-COVID-19 symptoms, but we know that many delayed symptoms depend directly on the severity of the infection and the body's immune response. During such stress and inflammatory cytokine secretion, the body stops or slows the hair growth cycle and directs energy to vital body structures. In most cases, hair loss occurs 2 to 3 months after infection and takes 3-4 months to start regrowth. Therefore, clinicians should be aware of the link between this infection and this pattern of hair loss. This pandemic has brought us closer to understanding the multiple treatment goals in TE and potential identification of therapy protocols.

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