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Research paper

A comprehensive review of etiology, pathophysiology epidemiology, and management of hair loss and its correlation with COVID-19

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Abstract

This paper explores the connection between COVID-19 and hair loss, emphasizing its emotional impact. Beyond respiratory effects, the virus causes various skin symptoms, including hair loss (telogen effluvium) in up to one-fifth of patients. The study reviews disruptions in the hair growth cycle induced by COVID-19, suggesting a multifactorial mechanism involving proinflammatory cytokines, the ADE phenomenon, and coagulation cascade activation. Recognizing the psychological impact, the paper uses a comprehensive research methodology to explore the correlation between hair loss and COVID-19. Recommendations for managing COVID-19-induced hair loss include counseling, dietary adjustments, and treatment options like minoxidil and corticosteroids. The study highlights the proactive role of healthcare professionals in addressing COVID-19-related hair loss to enhance patient satisfaction and overall quality of life.

Keywords: *Hair Loss; COVID-19; Pathophysiology; Management.*

1. Introduction

In 2019, the advent of acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) in Wuhan resulted in a global health crisis, known as the coronavirus disease 2019 (COVID-19) pandemic[1]. While COVID-19 is chiefly associated with respiratory and cardiovascular effects, it soon became evident that the virus's impact extended beyond the respiratory system, including the skin and hair[2], [3]. Patients exposed to COVID-19 experienced a vast spectrum of skin symptoms such as maculopapular rash, vesicular rash, urticaria, petechia, purpura, simultaneous herpetic lesions, ischemia, and hair loss[4]. Many studies reveal that after recovering from their illness, approximately 80% of individuals who survived COVID-19 continue to experience one or more non-respiratory symptoms for weeks or months [5]. COVID-19 survivors on social media have started calling the ongoing symptoms "long COVID" While academic literature refers to it as "post-acute COVID-19" (symptoms persisting for more than three weeks from the onset of initial symptoms) or "chronic COVID-19" (symptoms lasting for more than 12 weeks) [6]. Those affected are often called “Long Haulers”[7]. Interestingly, skin rashes associated with COVID-19 typically do not persist over time; however, only 3% of patients reported having a rash six months after being infected[8]. Note that up to one-fifth of patients with chronic COVID-19 experience hair loss [9].

Hair loss often occurs because of acute illnesses or autoimmune factors [10]. It has previously been noted that hair loss can be a symptom of severe respiratory diseases such as acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [11]. The range of hair loss, known as alopecia, observed in COVID-19 is widespread and includes all types of non-scarring alopecia [12]. Among these, telogen effluvium (TE) has attracted significant attention as a common non-scarring, self-limited form of hair loss characterized by diffuse shedding (more than 100 shed hair daily). The acute type typically occurs three months after the initial triggering event and can last up to six months. Chronic TE, on the other hand, persists for more than six months [13]. It is usually triggered by various stressors such as severe illness, traumatic events, medications, hormonal imbalances, and nutritional deficiencies [14].

Hair loss understanding relies on the hair growth cycle's three phases: anagen (long growth), catagen (brief transition), and telogen. About 85% of hair is in the anagen phase, while catagen is a short resting period lasting one to two weeks. Finally, the telogen phase or resting period spans three to five weeks before returning to anagen [15]. Disruptions in this cycle, such as those induced by COVID-19, can result in TE characterized by excessive daily hair loss as follicles abruptly shift from anagen to telogen [16].

Beyond TE, COVID-19 is linked to other forms of alopecia. In androgenic alopecia (AGA), the most common type, characterized by shortened anagen phases and miniaturized follicles, there's an increase in telogen follicles [17].

Hair and skin disorders have a notable impact on patients’ quality of life and satisfaction from a psychological perspective, leading to anxiety and depression [18]. Accordingly, there is a possibility that COVID-19 can cause or worsen alopecia due to psychological factors [19]. This highlights the importance of promptly and effectively addressing these conditions to improve patients' mental health and overall well-being. In this study, we conducted a comprehensive review to clarify the characteristics of HL complications associated with post-acute COVID-19 recovery, its mechanism, and therapeutic options.

2. Contributor qualifications

The authors of this manuscript all are medical doctors and their collective experience as interns during the COVID-19 pandemic in dermatology and infectious diseases wards uniquely qualifies them to investigate and discuss the correlation between COVID-19 and hair loss. The experience with real cases struggling with this problem ensures a comprehensive and insightful perspective on the subject.

3. Methods

In our research, we extensively searched PubMed and Google Scholar using keywords like "hair loss," "alopecia," and "COVID-19," along with Mesh terms. Our approach included original studies, reviews, editorials, and case reports, focusing on the relationship between hair loss and COVID-19, and treatment plans. We ensured completeness by examining references through citation analysis. Data extraction was systematic, involving key information extraction with consistency checks. Synthesizing the data included thematic analysis for patterns and trends, offering a nuanced understanding of the correlation between hair loss and COVID-19 from diverse perspectives and evidence types.

4. Hair loss

Alopecia is defined as the absence or loss of hair at a site expected to be observed [20]. Hair loss affects both sexes and all age groups and can be localized or diffuse, not to mention it can also be temporary or permanent. It is a clinical manifestation of various underlying diseases and is classified as scarring (cicatricial) or nonscarring. It can cause significant distress, leading to decreased quality of life. To diagnose the underlying disease, an exact history, careful physical examination, and focused evaluation are required.

5. Etiology

5.1. Non-scarring alopecia

This type of alopecia is more common in daily practice. In this group of alopecia, hair follicles remain intact; thus, hair loss is temporary and hair regrowth can be observed. This group includes androgenic alopecia (AGA), telogen effluvium (TE), alopecia areata (AA), anagen effluvium, traction alopecia, trichotillomania, and alopecia syphilitica.

- AGA is also known as hereditary hair loss, male balding, and female pattern alopecia. As we understand more about this condition, MPHL and FMHL are more widely accepted [21], [22]. This pattern of hair loss is the most common type in both genders and is usually slowly progressive. Men are usually affected in these scalp sites: the vertex, bitemporal, and mid-frontal, whereas women are usually affected in the center of the scalp, and frontal hairline involvement is uncommon [20], [21], [23-26].
- AA is a chronic autoimmune disease mostly characterized by acute initiation of hair loss on the scalp in a patchy pattern that affects both genders and all ages. Patients rarely have diffuse scalp hair loss (totalis) or hair loss of the entire body (universalis). This disease can present as a single episode or a remission and recurrence pattern [20], [24-27].
- TE occurs when the transition from the anagen to the telogen phase is disrupted. Triggering events include psychological or physical stress, chronic disease, pregnancy or postpartum, infection, malnutrition, surgery, endocrine or metabolic disorders, and drugs such as antidepressants, anticoagulants, anticonvulsants, OCPs, and retinoids[20, 24, 26]. This type of alopecia is noninflammatory, self-limited, acute, or chronic and affects both genders and all age groups. The mentioned etiologies can lead to telogen effluvium after approximately 3 months and last for 6 months[14].

5.2. Scarring alopecia

Irreversible damage occurs to the hair follicles in this alopecia group, causing permanent hair loss. This group is classified as primary or secondary. The primary scarring alopecia class includes lymphocytic (including lichen planopilaris (LPP), frontal fibrosing alopecia (FFA), central centrifugal cicatricial alopecia, discoid lupus erythematous and others), neutrophilic (dissecting cellulitis and folliculitis decalvans) and mixed[28]. The most common types of scarring alopecia are FFA and LPP.

Secondary scarring alopecia is caused by some underlying diseases such as localized scleroderma, neoplasm, pemphigoid, infections, radiation therapy, and physical or chemical trauma [29].

5.3. Epidemiology

AGA is the most prevalent type of hair loss, affecting up to 80% of men and half of women[30]. Also, the prevalence of AGA increases with age in both genders. The rate of AGA is higher in Caucasians than in Afro-Americans and Asians. The prevalence of AA is estimated to be 0.2% of the general population, and approximately 2% of the population experiences AA during their lifetime. It is more common between 10 and 25 years (60%)[30-32]. A multicenter retrospective study was conducted by Vano-Galvan et al. in 2019 to investigate the prevalence of the types of hair loss in patients referring to dermatology clinics[33]. The result was 73% nonscarring (AGA 37.7%, AA 18.2%, TE 11.3%) and 27% scarring (FFA 10.8%, LPP 7.6%) in over 3000 patients diagnosed with alopecia.

5.4. History and physical examination

To evaluate alopecia and plan appropriate treatment, a thorough history including the following items is necessary: time of hair loss onset, progression, time course, distribution, other symptoms, diet history, family history, recent medications, and gynecological and obstetrics history of females[20]. Scalp, face, and nails should be inspected and examined properly, and some manifestations such as papules, erythema, pustules, scaling, nail discoloration, and crusting should be assessed (48). The dermoscope plays a vital role in visualizing hair structures that are invisible to the eye. The hair pull test is helpful in hair loss evaluation. In addition, examination of the extracted hair using a microscope can determine the phase [24], [25].

5.5. Non-scarring alopecia

AGA affects the vertex, bitemporal, and midfrontal areas in males and the central scalp in females. The hair pull test is commonly negative and shows telogen roots (roots with club-shaped bulbs). In dermoscopy, several vellus hairs, the difference in hair thickness, perifollicular pigmentation, and yellow dots can be seen[21], [26]. AA commonly presents with a patchy pattern of hair loss on the scalp. No inflammation or scarring was observed in the affected skin. A positive hair pull test indicates an active phase of hair loss. A pathognomonic manifestation of AA is observed in the periphery of active lesions as exclamation mark hairs[26], [27]. Patients with TE usually complain of hair loss of the entire scalp. In the active phase, a positive hair pull test was observed at many sites. Anemia due to iron deficiency and thyroid disorders are 2 comorbidities commonly associated with TE[34]. Dermoscopy can distinguish chronic TE from FMHL, with greater variability in hair diameter in FMHL [14], [35].

5.6. Scarring alopecia

Vano-galvan et al. and Tolkachov et al. proposed diagnostic criteria for FFA. 2 major or 1 major with 2 minor criteria suggest the diagnosis of FFA [36], [37].

The major criteria are 1. Scarring alopecia in the temporal, frontal, or frontotemporal sites of the scalp without follicular keratotic papules on the body, 2. Diffuse bilateral alopecia of the eyebrow.

Minor criteria are 1. Perifollicular erythema, follicular hyperkeratosis, or both in trichoscopy, 2. Histopathologic features of scarring alopecia on biopsy, 3. Involvement of the occipital area, facial hair, sideburns, and body hair as additional FFA sites, 4. Facial papules without inflammation.

Multiple patchy alopecic sites with pruritus, follicular hyperkeratosis, and perifollicular erythema on peripheral zones are the features of LPP, and this type is seen on the vertex. Anagen hair with thick roots may be seen in the pull test. With a dermoscopic examination of the scalp, peripilar casts, perifollicular erythema, scaling, and follicular keratotic plugs can be observed [29], [38].

Prognosis

- AGA is a progressive disorder that can lead to complete baldness in males; therefore, early recognition and treatment can preserve as much hair as possible[20].
- AA is unpredictable and usually involves relapses and remissions. Factors such as onset in childhood, long duration, nail involvement, and autoimmune comorbidities may lead to a worse prognosis[25].
- Hair loss in patients with TE can be reversed by removing the triggering factors
- FFA and LPP have unpredictable prognoses with many factors leading to worse or better prognoses.

6. Hair loss and COVID-19

COVID-19 is mainly an acute respiratory disease. However, this illness can present additional symptoms in other parts of the body, including the skin. Dermatologic manifestations of COVID-19 include herpetic lesions and alopecia [39]. However, there is not enough evidence regarding the relationship between hair loss and COVID-19. Hair loss following COVID-19 is variable and can present as chronic or acute TE, AA, or exacerbation of AGA [40].

There have been numerous studies on the correlation between COVID-19 and hair loss. Some population-based studies have shown that severe COVID-19 infection causes more hair loss and depigmentation [41]. However, some studies have shown other findings, including a lack of evidence regarding the relationship between COVID-19 and AA [42].

Abrantes et al. found that the onset of TE after COVID-19 was 45 days on average and is commonly self-limited [43]. In a systematic scoping review study performed by Czech et al., TE was the most common type of hair loss among COVID-19 patients [10]. Most patients (95%) experienced hair regrowth within a median of 5 months. In an observational cross-sectional study performed by Seyfi et al, approximately 24% of patients with COVID-19 infection experienced TE afterward as a dermatological manifestation [44]. In a systematic review by Hossuni et al, patients with COVID-19 experienced TE after an average of 74 days [45]. The average time of TE hair loss after COVID-19 is shorter than other triggering events according to these studies.

In another systematic study performed by Nguyen et al, AGA was identified as the most prevalent type of hair loss in COVID-19 with 30.7% prevalence, with TE being the second most common type [46]. However, all COVID-19 patients experiencing AGA had a preexisting diagnosis of the illness, like AA. In contrast, most COVID-19 patients with TE lacked a history of alopecia. Most patients with AGA were male (90%), whereas female predominance was observed in TE (81%) and AA (60%). The onset of TE in this study was similar to that in the Czech et al. study with an average of 56 days. TE was resolved in all patients within 1 to 6 months without treatment in most cases. In addition, Nguyen et al. proposed that AGA is a risk factor for severe COVID-19 rather than a sequela of the illness. Nguyen et al. showed that AA worsened with COVID-19 infection. However, other studies investigating the role of COVID-19 on AA report mixed findings[47-50]. Overall, these studies propose that AA may be a sign of COVID-19 infection, mostly appearing 1-2 months after infection; however, more studies are necessary to understand the underlying clinical course.

7. Proinflammatory cytokines

Initially, acute TE has many triggering factors, such as stress, drugs, hormonal imbalances, major surgeries, febrile illnesses, and nutritional deficiencies[44]. In COVID-19, fever is a common symptom, and many individuals experience noticeable hair loss a few months after illness recovery. Even those who did not develop a fever or have COVID-19 might still experience increased hair shedding [45]. Therefore, the intense release of proinflammatory cytokines results from viral infections. The inflammation involved in TE has been confirmed through the analysis of biopsies taken from transitional areas of patients' scalps, which show a significant presence of mononuclear cells and mast cells actively degranulating within the follicular sheaths. The activated fibroblasts in the affected sites produce collagen, which leads to the substitution of follicular technogenic elements with residual fibrotic sheaths (fibrous tracts). In response to viruses such as SARS-CoV-2, the body mounts robust antiviral defenses, particularly via interferon, a component of the body's antiviral response known to induce acute TE[51]. COVID-19 often leads to elevated levels of proinflammatory cytokines such as IL-1, IL-6, IL-2, IL-17, TNFα, IL-1β, and IFNγ, MCP-1, IP-10, and many more[2], [52], [53]. The early catagen phase, oxidative stress, and apoptosis of hair cells are caused by an abrupt surge of cytokines in the blood. Among these proinflammatory molecules, interleukin (IL)-6 holds a pivotal role, particularly in severe forms of COVID-19 [17], [54]. Elevated levels of IL-6 affect the hair follicles by disrupting their immune privilege, inducing the catagen phase, and inhibiting hair shaft elongation by suppressing matrix cell proliferation, inciting local inflammation [43], [55], [56]. Furthermore, high levels of IL-4, often observed in elderly COVID-19 patients, can regulate keratinocyte apoptosis in hair follicles, ultimately resulting in hair loss [57].

TE development may be initiated by a cytokine storm that damages matrix cells. Subsequently, hair follicles enter a quiescent state in response to biological stressors, such as excessive interferons (IFNs). Elevated levels of interferon, which are associated with acute TE, are often observed in COVID-19 patients [51]. WBCs infected by SARS-CoV-2 produce proinflammatory cytokines that play a critical role in the progression of COVID-19-related complications. A plausible mechanism for disrupting hair follicles is the involvement of monocytes [58].

Furthermore, an elevated number of NK lymphocytes in affected hair follicles or dermal papilla cells dependent on the JAK–STAT pathway may cause AA when the immune privilege of the hair follicle is compromised The onset of this condition is significantly influenced by genetic factors, with a notable percentage ranging from 10% to 20% of individuals who have relatives experiencing it [59]. The genes implicated in these cases are closely associated with modifications in genes responsible for immune and inflammatory responses, including but not limited to MHC, CTLA4, and PRDX5 [60].

8. Hair follicles damaged directly by a virus (ADE phenomenon)

This mechanism elaborates on hair follicles damaged directly by a virus, a hypothesis that may explain the early occurrence of TE after COVID-19. Initially, the virus attaches to host cells via spike glycoproteins of SARS-CoV-2, binding to ACE II. Later, non-neutralizing virus-specific antibodies (NAbs) seen in patients with COVID-19 can boost the entry of the virus into cells by interactions with complement receptors and Fcγ [61]. Some researchers have hypothesized that SARS-CoV-2 has a direct effect on hair follicles through the ADE phenomenon, a phenomenon previously reported for dengue virus and other coronaviruses such as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) [51] [62].

9. Cascade of coagulation and microthrombi formation

Higher levels of the mentioned cytokines leading to the proinflammatory state are usually seen in patients with severe COVID-19, potentially correlating with an increased risk of TE. An additional process that may trigger TE is the activation of the coagulation cascade that occurs in COVID-19[63]. This activation leads to a decrease in the concentration of anticoagulant proteins, contributing to the formation of microthrombi, that can obstruct the blood vessels of hair follicles, representing an alternative explanation for how TE can occur after COVID-19 [64], [65].

In addition, there are speculative considerations regarding the role of androgenic hormones and their receptors, which regulate the hair follicle cycle and may facilitate a direct effect of COVID-19 on hair follicles [66]. However, the use of medications in COVID-19 treatment, such as heparinoids, might have played a part in causing acute TE (98). Nevertheless, there is a disagreement in the available evidence when it comes to understanding how this happens. In the studies by Rossi et al. [51] and Rizzetto et al. [67], the likelihood of drug-induced acute TE in COVID-19 appears to be low. Rossi et al. argued that this was based on the early onset of acute telogen effluvium, whereas Rizzetto et al. emphasized the brief duration of COVID-19 treatment as a reason for its improbability.

Furthermore, additional stressors caused by the pandemic, such as social distancing and unemployment, can play a role in the development of hair loss[67].

10. Management

Hair plays an important role in human appearance, and hair loss can considerably affect one's quality of life, often leading to emotional distress and dissatisfaction with medical care [68]. Given that Telogen effluvium has emerged as the prevalent form of hair loss linked to COVID-19, as reported in studies indicating rising incidence rates after the pandemic declaration [58] [69]. It becomes crucial to emphasize the management of this prevalent alopecia subtype. Educating patients about their condition is crucial for effective disease management [16], and reassuring them that TE is temporary can be beneficial [70]. Hair holds significance in the human body, and the emotional impact of hair loss varies among individuals [16]. For certain individuals, the impact of hair loss can be as significant as that experienced with more serious chronic or life-threatening illnesses[68]. In the context of patients with elevated stress and anxiety levels, which notably surged during the COVID-19 pandemic [71], [72], stress remains a major contributor to telogen effluvium. Psychological counseling, as the least invasive and effective way to address emotional impact, can be a good and safe approach [14]. Physicians should inform patients that hair loss may persist for up to six months, although at a reduced rate. While some regrowth can occur shortly after addressing the trigger, achieving significant growth may take over a year [73]. Acute telogen effluvium usually resolves on its own; however, if there is a dietary imbalance, it needs to be addressed to promote hair regrowth [74]. For example, several studies have provided evidence indicating a potential correlation between decreased levels of vitamin D and TE [75], [76] and the impact of oral vitamin D on hair regrowth in those patients [77]. Good nutrition and healthy sleep patterns are also crucial for countering COVID-19-related hair loss by boosting the immune system. Key vitamins (A, B, C, D, E) and minerals such as iron and zinc in fresh foods, whole grains, meat, fish, low-fat dairy, and healthy fats support a robust immune system [78].

Recommendations for treating COVID-19-induced telogen effluvium have been contradictory. Some experts advise against treatment, noting that typical acute telogen effluvium typically improves naturally within six months [79], whereas others believe that we should consistently consider the available treatment options [80]. The choice of medications to manage acute TE varies among patients and across different studies, primarily to encourage hair regrowth. Topical minoxidil is the most frequently prescribed medication and has been used for more than three decades to treat various hair loss conditions [81] [45]. Furthermore, some studies have suggested that oral minoxidil, administered at doses ranging from 0.25 mg to 2.5 mg, demonstrates efficacy in addressing TE [20]. In addition, some dermatologists use topical corticosteroids for treatment, and if a patient experiences reduced trichodynia following their application, it indicates the efficacy of the treatment [16]. There is also evidence that platelet-rich plasma (PRP) can effectively treat TE. The PRP stimulates hair growth and maintains improvements for up to three months. Its safety profile is good, with no notable differences between PRP preparation methods [82]. In addition, in a case study investigating instances of TE following COVID-19 vaccination, mesotherapy treatments were applied, yielding substantial and rapid improvements, particularly in individuals diagnosed with TE [59].

We should note that one of the significant challenges in treating hair loss is patient noncompliance. To address this, strategies include recommending suitable treatments, simplifying medication regimens, using controlled-release products, prescribing safer medications, and educating patients about managing side effects when alternatives are limited [73].

11. Conclusion

This review has illuminated the complicated relationship between COVID-19 and hair loss, shedding light on an often-overlooked aspect of the aftermath of the pandemic. The impact of hair loss on individuals can extend far beyond its physical manifestations, often taking a toll on their emotional and psychological well-being. Recognizing the significance of this matter, it becomes crucial for physicians to be attuned to the potential challenges that their patients may face in the wake of COVID-19.

While it is reassuring that hair loss commonly associated with the virus typically resolves on its own, this does not diminish the importance of providing information and support to those affected. Equally vital is staying updated on the latest treatment options, enabling healthcare providers to offer proactive solutions for patients who may opt for intervention to alleviate their distress.

By taking a proactive approach to addressing COVID-19-related hair loss, healthcare professionals can play a crucial role in improving patient satisfaction and overall quality of life. We should consider, it is incumbent upon physicians to not only provide medical care but also offer guidance and assurance that can make a meaningful difference in the lives of their patients.

12. Conflict of interest

None.

13. Informed consent

Not applicable.

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Authors' contributions

FC, MA, and MF wrote the manuscript. LO corrected the manuscript for its scientific basis and revised the manuscript for grammar and syntax mistakes. All authors read and approved the final manuscript.

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