Chronic telogen effluvium reversal using *E. coli*-derived cytokines and growth factors: a case report

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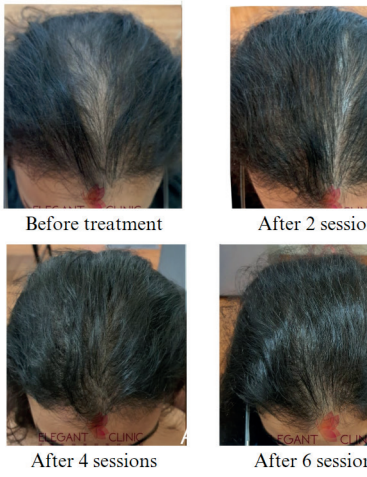

Figure 1: Central top view before treatment and after subsequent treatment sessions.

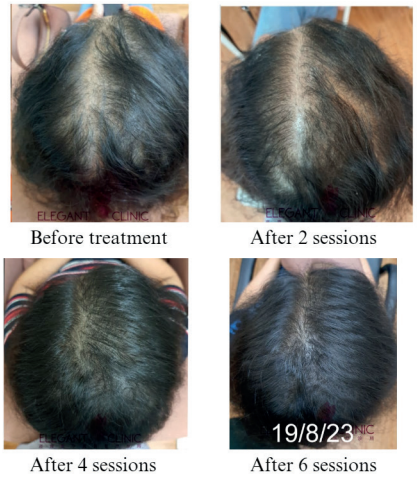

Figure 2: Vertex view before treatment and after subsequent treatment sessions.

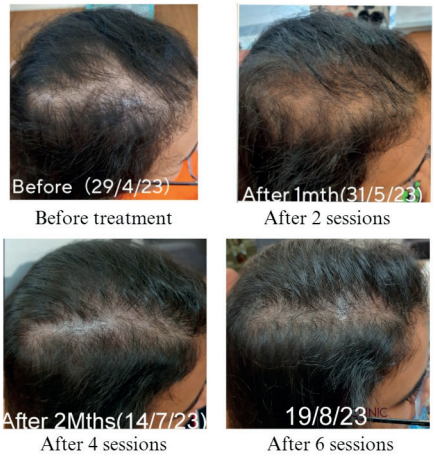

Figure 3: Frontotemporal view before treatment and after subsequent treatment sessions.

Chronic telogen effluvium (CTE) is a condition where there is prolonged increased hair shedding, primarily affecting middle-aged women. Its exact cause is often unknown. In CTE, many hair follicles enter the resting phase prematurely due to various reasons, leading to diffuse, non-scarring hair loss [1]. A related condition, short anagen syndrome, features abnormally short growth phases, leading to consistent hair shedding and difficulty in growing long hair. Historically, diffuse cyclical hair loss was an initial term describing periods of reversible hair shedding, which improved with corticosteroids [2]. The concept of telogen effluvium (TE) was introduced by Kligman, emphasising that various triggers cause hair follicles to end their growth phase early. The extent of TE depends on the duration and intensity of exposure to these triggers, with individual variations also playing a role [3]. While Headington identified five types of TE, Whiting saw CTE as its own primary category. Gilmore and Sinclair suggested that CTE may be secondary to a reduction in the variance of anagen representing a distinct functional type [2]. Chronic telogen effluvium is a challenging condition to manage as its underlying cause is not always clear and often multifactorial. New treatments are emerging for TE, including promising research into cytokines and growth factors. Here, we present a case study of a CTE patient treated with these bioactive agents.

Case report

A 26-year-old Indian lady of no known medical illness presented to the clinic with a history of hair loss since she was 18 years old and progressively worsened four years ago during a period of significant stress. Her hair loss was preceded by an alleged high degree of psychological stress and sleep pattern disturbances during the period of stress. While her menstrual cycle was regular initially, it became irregular four years ago likely due to the same stressors. She was started on hormonal treatment by her gynaecologist for the irregular menses. Around the same time, another dermatologist prescribed oral finasteride, oral minoxidil, and topical minoxidil spray to address her severe hair loss. She had previously sought treatment at a dermatology clinic where she was prescribed a course of oral steroids, oral finasteride, and both oral and topical minoxidil for eight months. However, she did not observe any significant hair growth or any improvement following these interventions.

On clinical examination, there was diffuse hair thinning and generalised hair loss, with no focal alopecia present. Moderate to severe hair recession was observed along the frontal temporal regions. The hair pull test was positive. The patient provided informed consent for the cytokines and growth factor therapy offered in the clinic. Figures 1, 2, and 3 illustrate her hair and scalp condition during her initial presentation to the clinic and after subsequent sessions, captured from three views.

The patient was started on treatment with cytokines and growth factors derived from *Escherichia coli* bacteria. The product is in the form of a solution. The key ingredients of the product include fibroblast growth factor 9 (FGF9), keratinocyte growth factor (KGF), insulin-like growth factor 1 (IGF1), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), Noggin (NOG) protein, superoxide dismutase (SOD), and adenosine triphosphate (ATP).

Radio-frequency (RF) microneedling was conducted, followed by the topical application of the product. The RF system was set to a continuous wave with a pulse duration of 120msec, a depth of 1.5mm, and power at level 4, executed in two passes. Subsequently, the system was adjusted to power level 1 and depth 0.8mm, and another two passes were performed. The solution was then topically applied to the treated

scalp. This enhances the absorption of the solution.

The procedure was done once a month for a total of eight sessions. At the time of writing, she had completed six of the eight sessions. Four months after the onset of treatment, there was a noticeable improvement in her hair volume and less evident scarcity along her hair partition, as shown in Figures 1–3. The pretreatment and posttreatment trichoscopy analyses showed improvements in hair regrowth, hair thickening, and the promotion of follicular units. Additionally, there was a reduction in yellow dots. Collectively, these effects result in an increase in the hair area coverage index, which reflects a noticeable cosmetic change and hair thickening.

Discussion

Despite CTE being a condition more commonly observed in middle-aged women, there are reports of occurrences in younger women, although confirmatory prevalence studies are lacking. For instance, a clinical study reported that approximately 6 out of 180 women suffered from CTE [4]. At present, there are no definitive treatments for CTE, and surgical hair transplantation is not recommended. In this patient's case, further exploration of the causes of her stress may help identify if it can be relieved through psychological or psychiatric treatments.

Stress can affect the hair growth cycle in several ways, including affecting immune response [5] and hormone fluctuations [6]. When the cause for CTE cannot be identified, minoxidil remains a consideration for medical treatment [7]. The lack of targeted treatment is due to the fact that the pathophysiology of CTE has not been defined. However, since CTE is linked to a disruption in the hair growth cycle, many studies focus on the hair follicles located in the scalp. Ongoing research is trying to understand both the underlying pathophysiological mechanisms and potential treatments for CTE. Current clinical studies on TE have pointed out several potential therapeutic targets for CTE. These include nutritional supplementation [8], biologics [9], biochemicals, herbal remedies [10,11], and nano-formulated products to enhance bioavailability [12].

In this case report, we discuss a patient who has experienced prolonged hair loss without a specific cause which has led to her diagnosis of idiopathic CTE. Given the various treatments she had tried over the years, she was a suitable candidate for emerging CTE treatments, such as the product highlighted in this report. Based on the product's ingredients, these biologics and biochemicals each offer unique properties related to scalp health restoration and hair growth promotion.

Studies have shown that VEGF stimulates hair growth by promoting angiogenesis, facilitating nutrient delivery to hair follicles which increases in follicular diameter [13]. In vivo research indicates KGF might protect hair follicle stem cells, boosting epithelial regeneration after damage [14]. In a clinical study involving 23 women with telogen effluvium, the growth factors VEGF and KGF were observed to have reduced expression in the scalp, at relative areas of expression of 25.79% and 35.83% respectively. In comparison, healthy women showed expression levels of 68.53% for VEGF and 47.68% for KGF [15]. Fibroblast growth factors are proteins involved in cellular processes. They are shown to promote hair growth by inducing the anagen phase in dormant hair follicles [16]. For instance, FGF9 can induce hair follicle neogenesis in vivo [17]. And bFGF, also known as fibroblast growth factor 2, is a mitogenic cytokine with the potential to induce an earlier anagen phase and prolong mature anagen phase [16].

Basic fibroblast growth factor supports skin and wound healing by enhancing the proliferation and differentiation of keratinocytes and fibroblasts. By binding to specific cell receptors, bFGF stimulates the proliferation and migration of these cells, essential for tissue repair and skin integrity. Furthermore, bFGF reduces alpha-smooth muscle actin expression, diminishing myofibroblast presence in wounds, which can mitigate excessive scarring. Additionally, bFGF promotes the synthesis of extracellular matrix proteins, including type I collagen and elastin, which are important for skin strength and elasticity [18].

Insulin-like growth factor 1 has been shown to regulate hair follicle proliferation, tissue remodelling, and the hair growth cycle. Case studies on IGF1 and alopecia have demonstrated that such patients often have a deficiency in the level of this protein [19]. Noggin is a glycoprotein secreted by mesenchymal cells. It antagonises bone morphogenetic protein (BMP) activity [20]. In an in vivo study, Noggin was demonstrated to induce new hair growth phases in hair follicles within 5–18 days. This was achieved by neutralising the inhibitory activity of bone morphogenetic protein 4 (BMP4) using the BMP antagonist. Typically, BMP4 inhibits hair growth in postnatal skin [21]. Oxidative damage to hair follicles contributes to androgenetic alopecia, and SOD has the potential to counteract such damage.

In a clinical study of 52 patients with androgenetic alopecia, there was a statistically significant reduction in SOD activity levels in red blood cells compared to controls [22]. Adenosine, derived from adenosine triphosphate, promotes hair growth by activating specific receptors, leading to the release of growth factors in cells involved in hair development. It also boosts certain pathways for hair follicle formation and renewal. Furthermore, in certain hair-related cells, adenosine increases energy production and other factors linked to hair growth stimulation [23].

As research on telogen effluvium advances, our understanding of its related biological mechanisms becomes more refined. Efforts to develop products for CTE treatment continue, with an emphasis on incorporating various biologics and biochemicals to benefit those affected by the condition. However, it is essential to study the interactions between these cytokines and growth factors. While each bioactive agent might individually promote hair growth, their combined effects might not yield the same results as when administered separately. Additionally, the chemical interactions between these factors and the preservation of their bioactive properties in a product should be evaluated, considering both the pharmacokinetics and dynamics. Nevertheless, for the benefit of patients, the safety and efficacy of any product should always be prioritised over meticulously detailed mechanisms.

In conclusion, the combined approach of cytokines, growth factors, and microneedling demonstrates promising potential in treating CTE. Further research is needed to elucidate the biological mechanisms and the interactions between the specific cytokines and growth factors that contribute to hair follicular health. Additionally, broader clinical trials are necessary to evaluate the efficacy across a diverse patient group and safety considerations including potential drug-drug interactions and implications on patients with other medical conditions.

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