Editorial Comment

Skin Appendage Disorders

Skin Appendage Disord 2016;2:39–44
DOI: 10.1159/000446119

Received: March 3, 2016
Accepted: March 29, 2016
Published online: May 21, 2016

Telogen Effluvium: Is There a Need for a New Classification?

Ralph M. Trüeb

Center for Dermatology and Hair Diseases Professor Trüeb, Wallisellen, Switzerland

The problems are solved, not by giving new information, but by arranging what we have known since long.
Ludwig Wittgenstein (1889–1951)

Few dermatologic problems carry as much emotional overtones as hair loss, particularly in women complaining of diffuse hair loss, at times associated with a peculiar scalp dysesthesia (trichodynia). Adding to the patient's worry may be prior frustrating experiences with physicians who tend to trivialize complaints of hair loss or dismiss them completely. This attitude on the part of physicians may result from a lack of understanding the patient on the emotional level, or from a lack of knowledge of the underlying pathophysiology and the best available evidence gained from the scientific method for clinical decision making and treatment on the technical level. As with any medical problem, the patient complaining of hair loss requires a comprehensive medical and drug history, physical examination of the hair and scalp, and appropriate laboratory evaluation to identify the cause. The clinician also has a host of diagnostic techniques that enable the classification of the patient's disorder as a shedding disorder or a decreased density disease as well as the documentation of true or only perceived pathology. Inexperienced physicians are encouraged to refer to the respective newer textbooks on successful treatment of female and male alopecia [1–4]. The prerequisite for delivering appropriate patient care is an understanding of the pathologic dynamics of hair loss and a potential multitude of causal relationships. Once the diagnosis is certain, treatment appropriate for that diagnosis is likely to control the problem. Ultimately, the best way to alleviate the emotional distress related to hair loss is to effectively treat it.

Diffuse shedding of hair was originally termed 'defluvium capillorum'. As early as 1932, Sabouraud restricted the term to a sudden diffuse loss of hair following a severe emotional shock, while others applied it to all forms of alopecia [5]. In the 1950s, chronic diffuse alopecia in women was first differentiated from acute and reversible diffuse alopecia, attributable to a readily identifiable cause, and, in 1960, Sulzberger et al. [6] originally reported on an unexplained apparent increase in incidence of diffuse alopecia in women. However, the results of this questionnaire-based study do not allow discrimination between women with diffuse telogen effluvium or female androgenetic alopecia. Moreover, female androgenetic alopecia with its more diffuse thinning of the crown area and an intact frontal hairline, as opposed to male-pattern androgenetic alopecia with its characteristic bitemporal recession of the hair and balding vertex, was originally described by Ludwig [7] only in 1977. Ultimately, in the 1990s, Rushton et al. [8] and Rushton and Ramsay [9]

KARGER

E-Mail karger@karger.com
www.karger.com/sad

2296–9195/16/0022–0039$39.50/0

Ralph M. Trüeb, MD
Center for Dermatology and Hair Diseases Professor Trüeb
Bahnhofplatz 1A
CH–8304 Wallisellen (Switzerland)
E-Mail r.trueeb@derma-haarcenter.ch

characterized a majority of affected women biochemically and trichologically as having a diffuse androgen-dependent type of alopecia (androgenetic alopecia).

Nevertheless, a peculiar type of chronic telogen effluvium does seem to exist that preferentially affects women in their middle ages, and has probably originally been described in 1959 by Guy and Edmundson [10], who reported on a diffuse cyclic (type of) hair loss in women. The presentation of this type of diffuse hair loss tends to be distinctive: the typical patient is a vigorous otherwise healthy woman with a full, thick head of hair. Patients are adamant that they previously had more hair and are distressed by the prospect of going bald, and many bring large balls of hair for inspection, but despite this do not show any obvious balding. On examination, there is some bitemporal thinning and a positive hair pull test equally over the vertex and occiput. There is no widening of the central part, as in androgenetic alopecia. Ultimately, in 1996, Whiting [11] additionally characterized the histopathologic features of the condition finally delineating it from female androgenetic alopecia. In an attempt to find a simple method to reliably evaluate the diagnosis and activity of androgenetic alopecia and telogen effluvium, Guarrera et al. [12] adopted the modified wash test, which accomplishes such a task through the assessment of the number of shed hair and the vellus hair percentage. Five days after the last shampoo, the patient is instructed to wash the hair in the sink with its drain covered by a gauze. The hairs entrapped in the gauze are then counted. The collected hairs after washing are counted and divided into ≤3 and ≥5 cm in length. In female androgenetic alopecia, the proportion of vellus hairs is significantly higher than in chronic telogen effluvium (58.9 vs. 3.5%). And yet, the differential diagnosis of chronic telogen effluvium from androgenetic alopecia remains a challenge because of considerable overlap, with a proportion of 62.4% of 418 otherwise healthy women complaining of hair loss in one of our studies [13].

In 1961, Kligman [14] revealed the pathodynamics of one common pattern of response of hair follicles to a variety of insults and named it 'telogen effluvium'.

Whatever the cause, the follicle tends to behave in a similar way. To grasp the meaning of this generalization requires an understanding of the hair cycle and its derangements.

As originally proposed by American anatomist Mildred Trotter, the hair follicle is subject to constant turnover in the course of perpetual cycles through phases of proliferation in anagen, involution in catagen, and resting in telogen, with regeneration in the successive hair cycle. Cyclic hair growth activity occurs in a random mosaic pattern, with each follicle possessing its own individual control mechanism over the evolution and triggering of the successive phases, though systemic factors as well as external factors linked to the environment have an influence, such as: hormones, cytokines and growth factors, toxins, and deficiencies in nutrients, vitamins, and energy (calories). Since the original description of the hair growth cycle, additional phenomena relevant to hair growth and shedding have been recognized. In 1996, Guarrera and Rebora [15] observed that anagen hairs may fail to replace telogen hairs in androgenetic alopecia. By using the phototrichogram, a novel phenomenon was discovered: emptiness of the hair follicle following teloptosis. Guarrera and Rebora [16] chose to call this phenomenon 'kenogen', deriving from the Greek word for 'empty'. During kenogen, the hair follicle rests physiologically, but duration and frequency were shown to be greater in androgenetic alopecia, possibly accounting for baldness. In addition to the classical cycle, the hair follicle may follow an alternative route during which the telogen phase, not accompanied by a coincident new early anagen, ends with teloptosis leaving the follicle empty. In 2002, Stenn [17] recognized the shedding phase of the hair growth cycle, then renamed 'exogen', to be a uniquely controlled final step in the hair cycle involving a specific proteolytic step. Finally, in 2013, Bernard and colleagues [18] identified hypoxia markers in the human hair follicle stem cells and proposed hypoxia signaling mediated by the hypoxia-inducible transcription factor HIF1 to be important for reentry of the follicle into a new hair cycle in the course of a novel neomorphogenic hair cycle phase named 'neogen'. Therefore, besides the well-recognized systemic and external factors linked to the environment (hormones, cytokines, toxins, and nutrients), the local milieu at the level of the stem cells, such as hypoxia, has been recognized to also impact hair cycling.

Therefore, many factors can lead to pathologically increased hair loss. The pathologic dynamics of hair loss can be related to disorders of hair cycling, with telogen effluvium representing by far the commonest cause of hair loss. By definition, telogen effluvium results from a pathologically increased shedding of normal telogen hairs of >20%.

While a number of attempts have been made with respect to the underlying pathologic dynamics of telogen effluvium and its classification, original classification of the functional types of telogen effluvium by Headington [19] remains unabated the most comprehensive and is referred to in the most recent and pertinent textbooks on hair growth and disorders.

Table 1. Functional types of telogen effluvium with clinical correlations

In **immediate anagen release**, follicles that would normally complete a longer cycle by remaining in anagen prematurely enter telogen; it is a very common form of telogen effluvium, typically occurring after periods of physiologic stress. Because the shedding is dependent on transition from anagen through catagen and telogen with a subsequent release of telogen hairs, hair loss occurs 3–4 months after the inciting event; a host of different triggers has been implicated and identifies the clinical species of the genus, e.g. postfebrile, posttraumatic, postinterventional, psychogenic effluvium, and others; febrile illness, accidental trauma, or surgical operations with a large hemorrhage, a crash diet, or severe emotional distress are among the most common causes; most are self-limiting and will undergo normal reversal; a careful patient history with respect to the chronology of events usually reveals the diagnosis and the cause.
In **delayed anagen release**, hair follicles remain in prolonged anagen rather than cycling into telogen; when finally released from anagen, the clinical sign of increased shedding of telogen hair will be found. This type of telogen effluvium underlies postpartum hair loss; during the second half of pregnancy, the percentage of anagen hairs increases from the normal 85 to 95%; after parturition, the follicles, in which anagen has been prolonged, rapidly enter catagen and then telogen, with an increased shedding of hair evident after 3–4 months; most women will return to their usual hair growth cycle and prepregnancy thickness of hair between 6 and 12 months after birth; in case of persistent postpartum effluvium (>12 months), excessive hair loss may be caused by common conditions, such as female androgenetic alopecia, iron deficiency, or hypothyroidism; less common conditions include persistent hyperprolactinemia (Chiari-Frommel syndrome) and postpartum hypopituitarism (Sheehan syndrome) caused by pituitary necrosis due to blood loss and hypovolemic shock during childbirth.
In **immediate telogen release**, hair follicles normally programmed for release of telogen hairs after an interval of usually 100 days after the end of anagen are prematurely stimulated to cycle into anagen; there is premature teloptosis. This type of telogen effluvium underlies the seemingly ironic increased shedding of hair upon initiation of therapy with the topical hair growth-promoting agent minoxidil (shedding phase); patients should be prepared and informed that this represents a physiological response to treatment, since minoxidil not only increases the duration of anagen, but triggers an immediate telogen release.
In **delayed telogen release**, hair follicles remain in prolonged telogen rather than being shed and recycling into anagen; when finally teloptosis sets in, again the clinical sign of increased shedding of telogen hair is observed. This process underlies moulting in mammals and probably also seasonal shedding of hairs in humans or mild telogen effluvia following travel from low- to high-daylight conditions; it is likely that environmental factors, such as the photoperiod, mediate through the optic pathway and the neuroendocrine system hair coat phenotype and function to photoperiod-dependent environmental changes; we published a study of 823 otherwise healthy women with telogen effluvium observed over a period of 6 years and demonstrated the existence of overall annual periodicity in the growth and shedding of hair, manifested by a maximal proportion of telogen hairs in July; a second peak seemed to exist, although less pronounced, in April; the telogen rate was lowest towards the beginning of February [20]; the fact that human hair follicles, just as those of other mammals, undergo cyclical activity and are influenced by hormones, implies that human hair is not unaffected by these phenomena; from an evolutionary point of view, the maintenance of the low winter level of hair shedding and the postponement of hair fall until the end of summer might, perhaps, be postulated as having a selective advantage with respect to isolation of the head against the cold in winter, and protection of the scalp against the midday sun in summer, respectively.
Finally, existence of a **short anagen phase** was proposed by Headington [19], resulting in a mild form of persistent telogen effluvium in association with decreased hair length. Later, we confirmed the existence of short anagen hair as an isolated disorder in otherwise healthy children in an original report of two children with a peculiar type of isolated congenital hypotrichosis [21]; both presented with persistent short, fine hair since birth; shortening of the anagen phase of the scalp hair cycle leads to a decrease in the maximal hair length and an increase in the number of hairs in telogen, resulting in an increase in hair shedding; far more frequent is the acquired progressive shortening of anagen due to androgenetic alopecia (and probably senescent alopecia).
Modified from Headington [19].

On the basis of changes in different phases of the follicular cycle, Headington [19] proposed the classification of telogen effluvium into five functional types depending on changes in different phases of the hair cycle (table 1).

In the original description of Kligman [14], telogen effluvium is an acute diffuse hair loss brought about by a variety of triggers. Clinical experience, however, proves that chronic telogen effluvium also exists. It has arbitrarily been defined as diffuse telogen hair loss that persists longer than 6 months, and either represents a primary disorder and is then a diagnosis of exclusion, or it is secondary to a variety of identifiable systemic disorders; iron deficiency, thyroid disease, systemic lupus erythematosus, syphilis, HIV infection, dietary habits, and drugs are frequent culprits and must therefore be systematically investigated. The cause of chronic telogen effluvium may be multifactorial and often difficult to establish.

More recently, an inflammatory or 'autoimmune' type of telogen effluvium has been proposed on the basis of the observation of a high frequency of associated scalp dysesthesia (trichodynia), associated autoimmune phenomena (Hashimoto thyroiditis), and a response to topical corticosteroid treatment.

Rebora et al. [22] originally proposed the term 'trichodynia' for discomfort, pain, or paresthesia of the scalp related to the complaint of hair loss, and found a frequency of 34.2% of female patients who had their hair consultation because of hair loss. Our study on 403 patients (311 females, 92 males) whose main complaint was hair loss confirms that trichodynia affects a significant proportion of patients complaining of hair loss [23]. We found that 17% of patients complaining of this condition, i.e. 20% of female and 9% of male patients, reported 'hair pain', pain, or discomfort of the scalp, not otherwise explained by the presence of a specific dermatologic disease or neurologic disorder.

Statistical analysis failed to demonstrate any significant correlation between trichodynia, extent of hair thinning, and hair loss activity.

It is noteworthy though that trichodynia typically increases the anxiety related to the patient's preoccupation with hair loss or fear of hair loss. As opposed to the suggestion of Rebora et al. [22] that trichodynia would be typical for chronic telogen effluvium, the symptom did not allow any discrimination with respect to the cause of hair loss and was found in association with androgenetic alopecia as well.

The cause of trichodynia remains obscure. Rebora et al. [22] proposed a possible role of perifollicular microinflammation. Hoss and Segal [24] interpreted scalp dysesthesia as a cutaneous dysesthesia syndrome related to underlying psychiatric disorders, with affected individuals either suffering of depressive, generalized anxiety, or somatoform disorder. Hordinsky and colleagues [25] found localization of the neuropeptide substance P in the scalp skin of patients with painful scalp suggesting a causal relationship between the presence of substance P and trichodynia. Substance P represents a neuropeptide involved in nociception and neurogenic inflammation. More recently, a possible association with cervical spine disease has been reported [26]. Early on, we proposed that trichodynia probably is polyetiologic. Though only a small number of patients with trichodynia in the studied patients showed telangiectasia of the scalp, this finding strongly correlated with the presence of trichodynia. In this context, it is interesting to note that substance P not only represents an important mediator of nociception and neurogenic inflammation, but also exerts a potent vasodilatatory effect. The role of substance P and related substances (neuropeptides) in the pathogenesis of trichodynia, and especially its relation to the nervous system and emotional stress, need further elucidation. By the virtue of their bidirectional effects on the neuroendocrine and immune systems, substance P and other neuropeptides may well represent key players in the interaction between the central nervous system and the skin immune and microvascular system. Such mechanisms would explain the noxious effects not only of external stimuli (mechanical, thermal, and chemical), but also of emotional distress on cutaneous nociception through the release of neuropeptides, such as substance P. Interestingly, Paus and colleagues [27] demonstrated that stress-induced immune changes of the hair follicles in mice could be mimicked by injection of substance P in nonstressed animals and were abrogated by selective substance P receptor antagonism in stressed animals.

Up to date, histopathologic evidence is lacking for the presence of follicular inflammation in telogen effluvium or trichodynia.

In 2002, Sato-Kawamora et al. [28] suggested naming a peculiar type of inflammatory noncicatricial alopecia that is characterized by marked female predominance and a uniquely short clinical course 'acute diffuse and total alopecia of the female scalp'. It is basically identical with a subtype of alopecia areata presenting with diffuse hair loss as originally proposed in the German literature by Braun-Falco and Zaun [29] 40 years earlier in 1962. The condition usually affects women over 40 years of age who complain of diffuse alopecia and may be misdiagnosed as having telogen effluvium, and has also been des-

ignated 'alopecia areata incognita' (yet another synonymous designation for the same condition proposed by Rebora [30] in 1987). The presence of yellow dots and of short regrowing miniaturized hairs seen in the terminal hair-bearing scalp by trichoscopy, as well as associated autoimmune phenomena (Hashimoto thyroiditis and/or circulating antithyroid and antiparietal cell antibodies), represent important clues to the diagnosis. The diagnosis is usually confirmed by histopathology and/or an excellent response with complete hair regrowth to a course of systemic corticosteroids.

In the end, until proven otherwise, the designation 'inflammatory telogen effluvium' should be reserved exclusively for telogen effluvium resulting from inflammatory conditions of the scalp, such as severe seborrheic dermatitis, acute allergic contact dermatitis (usually to paraphenylenediamine in hair coloring agents), erythroderma (of psoriasis or lymphoma), or interface dermatitis from lupus erythematosus or dermatomyositis.

In summary, telogen effluvium represents a monomorphic reaction pattern of the hair follicle to a variety of causes. To grasp the meaning of this generalization requires a sound understanding of the hair cycle and its derangements. Headington's classification still represents the most rational of all proposals and has proven its validity, both for the understanding of the pathologic dynamics underlying hair loss and in clinical practice. It covers all clinical types of telogen effluvium, such as postfebrile, posttraumatic, and postinterventional telogen effluvium (immediate anagen release), postpartum telogen effluvium (delayed anagen release), shedding phase upon initiation of topical minoxidil treatment (immediate telogen release), and seasonal hair shedding (delayed telogen release). Moreover, Headington's ingenious classification predicted the existence of a short anagen syndrome, which was only later confirmed by clinical observation. The cause of primary chronic diffuse telogen effluvium remains obscure. It has been proposed that the disorder may be due to persistent or intermittent pathologic synchronization phenomena of the hair cycle, shortening of the anagen phase, or premature teloptosis. Up to date, histopathologic evidence is lacking for an inflammatory component or autoimmune origin. At least in cases associated with trichodynia, neuropeptide substance P may play a role. It remains a diagnosis of exclusion (disease, drugs, deficiencies), whereby it must be borne in mind that multiple-cause relationships may underlie this type of hair loss, including significant seasonal fluctuations of hair growth and shedding, potential overlap with androgenetic alopecia, and frequent psychological overlay [31].

Disclosure Statement

The author has no conflicts of interest to disclose.

References

1 Blume-Peytavi U, Tosti A, Whiting DA, Trüeb RM (eds): Hair Growth and Disorders. Berlin/Heidelberg, Springer, 2008.
2 Trüeb RM: Female Alopecia. Guide to Successful Management. Berlin/Heidelberg, Springer, 2013.
3 Trüeb RM, Lee W-S: Male Alopecia. Guide to Successful Management. Cham, Springer International Publishing Switzerland, 2014.
4 Trüeb RM: The Difficult Hair Loss Patient. Guide to Successful Management of Hair Loss and Related Conditions. Cham, Springer International Publishing Switzerland, 2015.
5 Rebora A: Telogen effluvium. Dermatology 1997;195:209–212.
6 Sulzberger MB, Witten VH, Kopf AW: Diffuse alopecia in women. Its unexplained apparent increase in incidence. Arch Dermatol 1960;81:556–560.
7 Ludwig E: Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. Br J Dermatol 1977;97:247–254.
8 Rushton DH, Ramsay ID, James KC, et al: Biochemical and trichological characterization of diffuse alopecia in women. Br J Dermatol 1990;123:187–197.
9 Rushton DH, Ramsay ID: The importance of adequate serum ferritin levels during oral cyproterone acetate and ethinyl oestradiol treatment of diffuse androgen dependent alopecia in women. Clin Endocrinol 1992;36:421–427.
10 Guy WB, Edmundson WF: Diffuse cyclic hair loss in women. Arch Dermatol 1960;81:205–227.
11 Whiting DA: Chronic telogen effluvium: increased scalp hair shedding in middle-aged women. J Am Acad Dermatol 1996;35:899–906.
12 Guarrera M, Cardo PP, Rebora A: Assessing the reliability of the Modified Wash Test. G Ital Dermatol Venereol 2011;146:289–294.
13 Bregy A, Trüeb RM: No association between serum ferritin levels >10 microg/l and hair loss activity in women. Dermatology 2008;217:1–6.
14 Kligman AM: Pathologic dynamics of human hair loss. 1. Telogen effluvium. Arch Dermatol 1961;83:175–198.
15 Guarrera M, Rebora A: Anagen hairs may fail to replace telogen hairs in early androgenic female alopecia. Dermatology 1996;192:28–31.
16 Guarrera M, Rebora A: Kenogen in female androgenetic alopecia. A longitudinal study. Dermatology 2005;210:18–20.
17 Stenn K: Exogen is an active, separately controlled phase of the hair growth cycle. J Am Acad Dermatol 2005;52:374–375.
18 Rathman-Josserand M, Genty G, Lecardonnel J, Chabane S, Cousson A, François Michelet J, Bernard BA: Human hair follicle stem/progenitor cells express hypoxia markers. J Invest Dermatol 2013;133:2094–2097.
19 Headington JT: Telogen effluvium. New concepts and review. Arch Dermatol 1993;129:356–363.

20 Kunz M, Seifert B, Trüeb RM: Seasonality of hair shedding in healthy women complaining of hair loss. Dermatology 2009;219:105–110.
21 Barraud-Klenovsek MM, Trüeb RM: Congenital hypotrichosis due to short anagen. Br J Dermatol 2000;143:612–617.
22 Rebora A, Semino MT, Guarrera M: Trichodynia (letter). Dermatology 1996;192:292–293.
23 Willimann B, Trüeb RM: Hair pain (trichodynia): frequency and relationship to hair loss and patient gender. Dermatology 2002;205:374–377.
24 Hoss D, Segal S: Scalp dysesthesia. Arch Dermatol 1998;134:327–330.
25 Ericson M, Gabrielson A, Worel S, Lee WS, Hordinsky MK: Substance P (SP) in innervated and non-innervated blood vessels in the skin of patients with symptomatic scalp. Exp Dermatol 1999;8:344–345.
26 Thornsberry LA, English JC 3rd: Scalp dysesthesia related to cervical spine disease. JAMA Dermatol 2013;149:200–203.
27 Arck PC, Handjiski B, Peters EM, Peter AS, Hagen E, Fischer A, Klapp BF, Paus R: Stress inhibits hair growth in mice by induction of premature catagen development and deleterious perifollicular inflammatory events via neuropeptide substance P-dependent pathways. Am J Pathol 2003;162:803–814.
28 Sato-Kawamura M, Aiba S, Tagami H: Acute diffuse and total alopecia of the female scalp. A new subtype of diffuse alopecia areata that has a favorable prognosis. Dermatology 2002;205:367–373.
29 Braun-Falco, Zaun O: Über die Beteiligung des gesamten Capillitiums bei Alopecia areata. Hautarzt 1962;13:342–348.
30 Rebora A: Alopecia areata incognita: a hypothesis. Dermatologica 1987;174:214–218.
31 York J, Nicholson T, Minors P, Duncan DF: Stressful life events and loss of hair among adult women, a case-control study. Psychol Rep 1998;82:1044–1046.