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Commentary

Hormones and clocks: do they disrupt the locks? Fluctuating estrogen levels during menopausal transition may influence clock genes and trigger chronic telogen effluvium.

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Abstract

Chronic telogen effluvium describes the clinical condition noted mostly in middle-aged women of increased, diffuse scalp hair shedding that is prolonged and often presents with a fluctuating course that may continue for years but does not lead to visible hair thinning. Despite its description almost 20 years ago, the underlying pathologic cause of CTE is yet to be identified. However the culmination of research in the field of hair biology and the burgeoning field of chronobiology may lead to exciting breakthroughs in our understanding of CTE. In this paper the current literature on CTE is reviewed and a hypothesis is put forth that CTE may be triggered by hormonal fluctuations and alterations in circadian control genes.

Keywords: chronic telogen effluvium, clock genes, estrogen

Introduction

In 1996 Whiting introduced the term “chronic telogen effluvium” to describe the clinical condition noted mostly in middle-aged women, of increased, diffuse scalp hair shedding [1]. This condition is distinct from acute telogen effluvium in that the shedding is prolonged >6months and often presents with a fluctuating course that may continue for 6-7 years [1, 2]. Unlike in androgenetic alopecia(AGA) or female pattern hair loss (FPHL), there is no notable or visible hair thinning or change in scalp hair density in CTE other than bitemporal recession in some patients [2-4]. Histology can also be useful in making the diagnosis of CTE. In horizontal sections of 4mm scalp biopsies, there is a higher ratio of terminal to vellus-like hairs in CTE compared to AGA [1, 5]. The anagen to telogen ratio in CTE is essentially the same as in normal scalp [1]. Despite its description almost 20 years ago, the underlying pathologic cause of CTE is yet to be identified. However, the culmination of research in the field of hair biology and the burgeoning field of chronobiology may lead to exciting breakthroughs in our understanding of CTE. In this paper the current literature on CTE is reviewed and a hypothesis is put forth that CTE may be triggered by hormonal fluctuations and alterations in circadian control genes.

Chronic telogen effluvium: a disturbance of the anagen phase

Classic, or acute telogen effluvium, was first described by Kligman in 1961 who introduced the concept that increased hair shedding could occur in response to a perturbation of the hair cycle [6]. In 1993, Headington put forth five functional types of telogen effluvia based on the idea that shedding could occur as a result of alterations in the *phases* as well as to the *duration* of the hair cycle [7]. These types included: 1. Immediate anagen release, 2. Delayed anagen release, 3. Short anagen, 4. Immediate telogen release, and 5. Delayed telogen release. Of interest, Headington noted that with type 3 effluvium, idiopathic shortening of anagen could lead to persistent shedding since with every 50% reduction in the duration of anagen there is a corresponding doubling of follicles in telogen [7]. Thus it was presumed that CTE was a result of shortened anagen cycles [4], but without hair follicle miniaturization. In contrast, in AGA/FPHL, there is both miniaturization of the hairs along with shortening of the anagen phase [1]. The clinical observation that CTE could result in shedding over a course of many years without any clinical thinning of the scalp seemed to confirm that CTE was a distinct entity and not a precursor to AGA [2, 8]. In 2010, Gilmore and Sinclair used a computational modeling tool called "follicular automaton" to show that a decrease in the *variance* of anagen duration reproduced the features of CTE with cyclical hair loss and only minimal hair loss, whereas a decrease in duration of anagen resulted in changes seen with AGA/FPHL [9].

Chronic telogen effluvium: a potential hormonal trigger

In the original description of 355 patients with CTE, only 10 men were identified, suggesting an overwhelming preponderance in women; the average age was 44 years [1]. Subsequent reports have suggested that CTE does not occur exclusively in older women [10, 11], but it does seem to occur more frequently (67%) in post-menopausal women [3]. The fact that men usually wear their hair short may prevent an awareness of increased shedding. In a report of 123 patients with CTE, there was a "good" response in 55% of the patients to a combination of 5% minoxidil solution and hormonal supplements (cyproterone acetate, +/- estradiol) [3].

Women may uniquely encounter various hormonal and physiologic changes that can lead to alterations in the appearance, quality, quantity, and cycling of the hair fiber and hair follicle. Clinical observations have suggested that the use of oral contraceptives, their cessation, or hormone replacement therapy, may cause a temporary hair shedding [12]. During pregnancy there is an increase in hair growth rate, diameter, and ratio of anagen to telogen hairs that frequently leads to a post-partum telogen effluvium [13-15]. The post-menopausal period is another period when women may have changes in hair growth parameters. In a comparison of hair growth characteristics, the anagen to telogen ratio was decreased in post menopausal women compared to premenopausal women, both in those with and without a self-perceived change in hair density [16].

The major change that occurs with menopause is the near cessation of ovarian estrogen production. However, in recent years it has become clear that perimenopause or the transitition to menopause spans a variable period of time when estrogen levels can be erratic before they decrease to the low stable levels of menopause [17]. This transitional phase occurs on average 5 years prior to the onset of actual menopause, but can start as early as 10 years prior [18]. Certain environmental exposures such as smoking may hasten the onset of the transitional period [19]. Interestingly, in an analysis of 123 patients with chronic telogen effluvium, biochemical analysis revealed no significant abnormalities in values of estradiol, progesterone, androstenedione, and free testosterone for post-menopausal women; all the levels were in the low-normal range [3]. This finding is supportive of the concept that the actual level of estrogen or other hormones may not be correlated with hair shedding but rather a change or variance in levels may lead to CTE.

Although it has been recognized that estrogen is an important modulator of hair growth, the details of the molecular regulatory pathways have not been well characterized. Estrogen is synthesized in the ovary as well as in a number of peripheral tissues and acts via two estrogen receptors: alpha (ER alpha) and beta (ER beta), the later of which is the predominant receptor in the hair follicle [20, 21]. Several studies have demonstrated the influence of estrogen on the murine and other mammalian hair cycle, specifically that it causes premature catagen and prolonged telogen [22]. However, it is clear that the distribution, expression, and biologic activity of estrogen receptors in murine models may be quite different than in humans [23-30]. In vitro studies have shown that organ culture of human scalp hair follicles exposed to estradiol results in decreased growth, whereas cells of the in the dermal papilla responded with proliferation [31, 32]. Since hair growth and cycling are both influenced by numerous hormones, growth factors, transcription factors, and cytokines, many of which are known to be modulated by estrogens, it is plausible that an intricate orchestration of these pathways occurs in response to estrogen [33-35]. Thus in some women a period of erratic estrogen levels during the transition to menopause (albeit in the normal range) could alter hair growth and cycling and elicit episodes of chronic shedding, clinically seen as CTE.

Circadian clock genes and the hair follicle cycle

Almost all cells, including those of the hair follicle, have been shown to have an endogenous circadian clock [36]. These cell-based or peripheral clocks are synchronized by the master regulator, the suprachiasmatic nucleus that is located in the hypothalamus [36]. Circadian rhythms can be thought of as having a cyclical or oscillatory periodicity with variations in phases and amplitude [36]. These variations can by influenced by internal signals such as hormones and by external ones such as light [36]. The first gene identified to control circadian behavior was *Period(Per)* in 1971 [37]. Since then, chronobiologists have identified a number of other clock-related genes and have expanded our understanding of how these genes influence and regulate a number of biologic functions. Of interest to hair biology is that clock genes have been shown to regulate hair cycles [38-41].

The genes involved in regulating the circadian rhythm operate on a positive and negative feed back loop having a period of approximately 24 hours [39]. On a basic level, the positive feedback loop is controlled by CLOCK and BMAL1 genes, transcriptional activators, which heterodimerize and target the genes PER and CRY, which in turn heterodimerize and repress CLOCK/BMALI, thus creating the negative feedback [41]. It is not surprising that the hair follicle, which continuously cycles through periods of growth (anagen), regression(catagen), and relative quiescence (telogen), is regulated by variations in phases or amplitude of clock genes.

Our current understanding of the circadian clock genes in the hair follicle is based on in-vivo studies in both mouse and human models, as well as in-vitro experiments. Mice lacking the BMAL1 gene have an interruption in the onset of anagen hair [39] and analysis of clock genes from plucked hairs shows variations in gene expression with shift work [42]. There is also evidence that varying gene expression of clock genes regulates the transition of hair follicles from anagen to catagen and this periodicity is maintained in vitro organ culture in the absence of a central master regulator [38, 42].

It is known that the rhythmicity, or phase of cell-based clocks, can be influenced by internal signals such as hormones as well as external triggers such as light [36]. Specifically, it has recently been shown that in cultured human hair follicles, thyroxine (T4) differentially modulates expression of the peripheral molecular clock by upregulating expression of core clock genes BMAL1, PER1, CLOCK, CRY1, CRY2 [40]. Since estrogen and androgen receptors provide important input and feedback to both the central and peripheral clocks, sex differences are known to exist in circadian timing systems [36], and also likely influence the hair cycle.

Pathogenesis of CTE may relate to fluctuations in estrogens leading to alterations in hair follicle clock genes and disturbed hair cycling.

Despite being well characterized clinically and pathologically, the underlying pathogenesis of CTE is not fully understood. In CTE, underlying factors typically seen in acute telogen effluvium are not identified. One proposed explanation for the cyclical shedding of CTE is a change in the *variance* of anagen duration [9], though to our knowledge there are no known molecular signals that directly control such a variance. Estrogen is, however, involved in the regulation of the hair cycle and is an attractive candidate as an upstream signal that could trigger a variance in anagen duration. Specifically, estrogen has been shown to lead to premature catagen and prolonged telogen [22]. Moreover, hormonal feedback systems are known to influence the circadian timing system. Thus it is plausible that estrogen fluctuations paired with alterations in clock genes could lead to the cyclical and recurrent of shedding in CTE.

Further studies will be needed to ascertain the effect of estrogen on the circadian clock genes and a potential link to CTE.

References

1. Whiting DA. Chronic telogen effluvium: increased scalp hair shedding in middle-aged women. Journal of the American Academy of Dermatology. 1996;35(6):899-906. PubMed PMID: 8959948.
2. Sinclair R. Chronic telogen effluvium: a study of 5 patients over 7 years. Journal of the American Academy of Dermatology. 2005;52(2 Suppl 1):12-6. doi: 10.1016/j.jaad.2004.05.040. PubMed PMID: 15692504.
3. Garcia-Hernandez MJ, Camacho FM. Chronic telogen effluvium: incidence, clinical and biochemical features, and treatment. Archives of dermatology. 1999;135(9):1123-4. PubMed PMID: 10490125.
4. Whiting DA. Chronic telogen effluvium. Dermatologic clinics. 1996;14(4):723-31. PubMed PMID: 9238330.
5. Sinclair R, Jolley D, Mallari R, Magee J. The reliability of horizontally sectioned scalp biopsies in the diagnosis of chronic diffuse telogen hair loss in women. Journal of the American Academy of Dermatology. 2004;51(2):189-99. doi: 10.1016/S0190. PubMed PMID: 15280836.
6. Kligman AM. Pathologic dynamics of human hair loss. I. Telogen effuvium. Archives of dermatology. 1961;83:175-98. PubMed PMID: 13756813.
7. Headington JT. Telogen effluvium. New concepts and review. Archives of dermatology. 1993;129(3):356-63. PubMed PMID: 8447677.

8. Bittencourt C, Ferraro DA, Soares TC, Moraes AM, Cintra ML. Chronic telogen effluvium and female pattern hair loss are separate and distinct forms of alopecia: a histomorphometric and immunohistochemical analysis. Clinical and experimental dermatology. 2014;39(8):868-73. doi: 10.1111/ced.12406. PubMed PMID: 25156792.
9. Gilmore S, Sinclair R. Chronic telogen effluvium is due to a reduction in the variance of anagen duration. The Australasian journal of dermatology. 2010;51(3):163-7. doi: 10.1111/j.1440-0960.2010.00654.x. PubMed PMID: 20695853.
10. Rebora A. Telogen effluvium. Dermatology. 1997;195(3):209-12. PubMed PMID: 9407163.
11. Thai KE, Sinclair RD. Chronic telogen effluvium in a man. Journal of the American Academy of Dermatology. 2002;47(4):605-7. PubMed PMID: 12271308.
12. Bergfeld WF. Telogen Effluvium. In: Hordinsky Ma, editor. Hair and Scalp Diseases. New York: Informa Healthcare; 2008. p. 125.
13. Nissimov J, Elchalal U. Scalp hair diameter increases during pregnancy. Clin Exp Dermatol. 2003;28(5):525-30. Epub 2003/09/03. doi: 1331 [pii]. PubMed PMID: 12950345.
14. Lynfield YL. Effect of pregnancy on the human hair cycle. J Invest Dermatol. 1960;35:323-7. Epub 1960/12/01. PubMed PMID: 13764567.
15. Muallem MM, Rubeiz NG. Physiological and biological skin changes in pregnancy. Clin Dermatol. 2006;24(2):80-3. Epub 2006/02/21. doi: S0738-081X(05)00121-5 [pii] 10.1016/j.clindermatol.2005.10.002 [doi]. PubMed PMID: 16487877.
16. Robbins C, Mirmirani P, Messenger AG, Birch MP, Youngquist RS, Tamura M, et al. What women want - quantifying the perception of hair amount: an analysis of hair diameter and density changes with age in caucasian women. The British journal of dermatology. 2012;167(2):324-32. doi: 10.1111/j.1365-2133.2012.11010.x. PubMed PMID: 22524482.
17. Prior JC. Perimenopause: the complex endocrinology of the menopausal transition. Endocrine reviews. 1998;19(4):397-428. doi: 10.1210/edrv.19.4.0341. PubMed PMID: 9715373.
18. Burger H, Woods NF, Dennerstein L, Alexander JL, Kotz K, Richardson G. Nomenclature and endocrinology of menopause and perimenopause. Expert review of neurotherapeutics. 2007;7(11 Suppl):S35-43. doi: 10.1586/14737175.7.11s.S35. PubMed PMID: 18039067.
19. Gold EB. The timing of the age at which natural menopause occurs. Obstet Gynecol Clin North Am. 2011;38(3):425-40. doi: 10.1016/j.ogc.2011.05.002. PubMed PMID: 21961711; PubMed Central PMCID: PMCPMC3285482.
20. Thornton MJ, Taylor AH, Mulligan K, Al-Azzawi F, Lyon CC, O'Driscoll J, et al. Oestrogen receptor beta is the predominant oestrogen receptor in human scalp skin. Exp Dermatol. 2003;12(2):181-90. Epub 2003/04/19. doi: exd120209 [pii]. PubMed PMID: 12702147.
21. Thornton MJ, Taylor AH, Mulligan K, Al-Azzawi F, Lyon CC, O'Driscoll J, et al. The distribution of estrogen receptor beta is distinct to that of estrogen receptor alpha and the androgen receptor in human skin and the pilosebaceous unit. J Investig Dermatol Symp Proc. 2003;8(1):100-3. Epub 2003/08/05. doi: 10.1046/j.1523-1747.2003.12181.x [doi]. PubMed PMID: 12895004.
22. Hu HM, Zhang SB, Lei XH, Deng ZL, Guo WX, Qiu ZF, et al. Estrogen leads to reversible hair cycle retardation through inducing premature catagen and maintaining telogen. PloS one. 2012;7(7):e40124. doi: 10.1371/journal.pone.0040124. PubMed PMID: 22792225; PubMed Central PMCID: PMCPMC3390338.
23. Conrad F, Ohnemus U, Bodo E, Bettermann A, Paus R. Estrogens and human scalp hair growth-still more questions than answers. The Journal of investigative dermatology. 2004;122(3):840-2. doi: 10.1111/j.0022-202X.2004.22344.x. PubMed PMID: 15086574.
24. Stenn KS, Paus R, Filippi M. Failure of topical estrogen receptor agonists and antagonists to alter murine hair follicle cycling. J Invest Dermatol. 1998;110(1):95. Epub 1998/01/10. doi: 10.1046/j.1523-1747.1998.00077.x [doi]. PubMed PMID: 9424096.
25. Smart RC, Oh HS. On the effect of estrogen receptor agonists and antagonists on the mouse hair follicle cycle. J Invest Dermatol. 1998;111(1):175. Epub 1998/07/17. doi: 10.1046/j.1523-1747.1998.00257.x [doi]. PubMed PMID: 9665409.
26. Ohnemus U, Unalan M, Handjiski B, Paus R. Topical estrogen accelerates hair regrowth in mice after chemotherapy-induced alopecia by favoring the dystrophic catagen response pathway to damage. J Invest Dermatol. 2004;122(1):7-13. Epub 2004/02/14. doi: 22120 [pii] 10.1046/j.0022-202X.2003.22120.x [doi]. PubMed PMID: 14962083.
27. Oh HS, Smart RC. An estrogen receptor pathway regulates the telogen-anagen hair follicle transition and influences epidermal cell proliferation. Proc Natl Acad Sci U S A. 1996;93(22):12525-30. Epub 1996/10/29. PubMed PMID: 8901615.
28. Chanda S, Robinette CL, Couse JF, Smart RC. 17beta-estradiol and ICI-182780 regulate the hair follicle cycle in mice through an estrogen receptor-alpha pathway. Am J Physiol Endocrinol Metab. 2000;278(2):E202-10. Epub 2000/02/09. PubMed [PMID: 10662703]
29. Ohnemus U, Uenalan M, Conrad F, Handjiski B, Mecklenburg L, Nakamura M, et al. Hair cycle control by estrogens: catagen induction via estrogen receptor (ER)-alpha is checked by ER beta signaling. Endocrinology. 2005;146(3):1214-25. Epub 2004/12/14. doi: en.2004-1219 [pii] 10.1210/en.2004-1219 [doi]. PubMed PMID: 15591132.
30. Moverare S, Lindberg MK, Faergemann J, Gustafsson JA, Ohlsson C. Estrogen receptor alpha, but not estrogen receptor beta, is involved in the regulation of the hair follicle cycling as well as the thickness of epidermis in male mice. J Invest Dermatol. 2002;119(5):1053-8. Epub 2002/11/26. doi: 0637 [pii] 10.1046/j.1523-1747.2002.00637.x. PubMed PMID: 12445192.
31. Kondo S, Hozumi Y, Aso K. Organ culture of human scalp hair follicles: effect of testosterone and oestrogen on hair growth. Arch Dermatol Res. 1990;282(7):442-5. Epub 1990/01/01. PubMed PMID: 2078048.

32. Conrad F, Ohnemus U, Bodo E, Biro T, Tychsen B, Gerstmayer B, et al. Substantial sex-dependent differences in the response of human scalp hair follicles to estrogen stimulation in vitro advocate gender-tailored management of female versus male pattern balding. J Investig Dermatol Symp Proc. 2005;10(3):243-6. Epub 2005/12/31. doi: 10.1111/j.1087-0024.2005.10115.x [doi]. PubMed PMID: 16382674.
33. Conrad F, Paus R. Estrogens and the hair follicle. J Dtsch Dermatol Ges. 2004;2(6):412-23. Epub 2005/11/12. PubMed PMID: 16281598.
34. Ohnemus U, Uenalan M, Inzunza J, Gustafsson JA, Paus R. The hair follicle as an estrogen target and source. Endocrine reviews. 2006;27(6):677-706. doi: 10.1210/er.2006-0020. PubMed PMID: 16877675.
35. Thornton MJ. Oestrogen functions in skin and skin appendages. Expert Opin Ther Targets. 2005;9(3):617-29. Epub 2005/06/14. doi: 10.1517/14728222.9.3.617. PubMed PMID: 15948678.
36. Bailey M, Silver R. Sex differences in circadian timing systems: implications for disease. Front Neuroendocrinol. 2014;35(1):111-39. doi: 10.1016/j.yfrne.2013.11.003. PubMed PMID: 24287074; PubMed Central PMCID: PMCPMC4041593.
37. Konopka RJ, Benzer S. Clock mutants of Drosophila melanogaster. Proc Natl Acad Sci U S A. 1971;68(9):2112-6. PubMed PMID: 5002428; PubMed Central PMCID: PMCPMC389363.
38. Al-Nuaimi Y, Hardman JA, Biro T, Haslam IS, Philpott MP, Toth BI, et al. A meeting of two chronobiological systems: circadian proteins Period1 and BMAL1 modulate the human hair cycle clock. The Journal of investigative dermatology. 2014;134(3):610-9. doi: 10.1038/jid.2013.366. PubMed PMID: 24005054.
39. Lin KK, Kumar V, Geyfman M, Chudova D, Ihler AT, Smyth P, et al. Circadian clock genes contribute to the regulation of hair follicle cycling. PLoS Genet. 2009;5(7):e1000573. doi: 10.1371/journal.pgen.1000573. PubMed PMID: 19629164; PubMed Central PMCID: PMCPMC2705795.
40. Hardman JA, Haslam IS, Farjo N, Farjo B, Paus R. Thyroxine differentially modulates the peripheral clock: lessons from the human hair follicle. PloS one. 2015;10(3):e0121878. doi: 10.1371/journal.pone.0121878. PubMed PMID: 25822259; PubMed Central PMCID: PMCPMC4379003.
41. Geyfman M, Andersen B. Clock genes, hair growth and aging. Aging (Albany NY). 2010;2(3):122-8. PubMed PMID: 20375466; PubMed Central PMCID: PMCPMC2871241.
42. Akashi M, Soma H, Yamamoto T, Tsugitomi A, Yamashita S, Yamamoto T, et al. Noninvasive method for assessing the human circadian clock using hair follicle cells. Proc Natl Acad Sci U S A. 2010;107(35):15643-8. doi: 10.1073/pnas.1003878107. PubMed PMID: 20798039; PubMed Central PMCID: PMCPMC2932591.