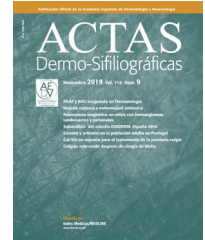




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PRACTICAL DERMATOLOGY

[Translated article] Dermatology Update on the Challenging Trichodynia



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Chemotherapy-induced alopecia

Abstract Trichodynia is the sensation of pain in the scalp, which, in most cases, is associated with certain types of alopecia. Despite being a term coined by Rebora back in 1996 to described patients with diffuse alopecia consistent with telogen effluvium, this symptom has currently been reported in other entities. Androgenic alopecia, scarring alopecia, alopecia areata, trichotillomania, and chemotherapy-induced alopecia are common causes of trichodynia. Similarly, its association with psychiatric comorbidities, including depression, anxiety, obsessive-compulsive disorder and somatoform disorders has been reported with a higher prevalence among women. Although its pathogenesis is still to be elucidate, some factors involved are substance P, psychiatric comorbidities and perifollicular inflammation. Clinically it exhibits pain or discomfort of the scalp, almost always in association with hair loss. The sensation of pain can occur throughout the scalp or locally in some specific areas. Diagnosis is clinical and one of exclusion. Regarding treatment, there are no specific therapies for trichodynia. However, the use of botulinum toxin A, antidepressants, neuromodulators, propranolol, topical corticosteroids, oral corticosteroids and topical cannabinoids are therapeutic alternatives that should be taken into consideration. Since treatment of trichodynia is still therapeutically challenging for dermatologists more prospective studies are needed to evaluate new therapies.

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PALABRAS CLAVE

Efluvio telógeno;
Alopecia cicatricial;
Alopecia areata;
Tricotilomanía;
Alopecia por
quimioterapia

Actualización de la tricodinia, un reto para los dermatólogos

Resumen La tricodinia es la sensación de dolor en el cuero cabelludo, en asociación con algunos tipos de alopecias. A pesar de ser un término acuñado por Rébora en 1996 en los pacientes con alopecia difusa compatible con efluvio telógeno, en la actualidad se ha reportado este síntoma en otras entidades. La alopecia androgénica, las alopecias cicatriciales, la alopecia areata, la tricotilomanía y la alopecia inducida por quimioterapia son causas comunes de tricodinia. Asimismo, su relación con comorbilidades psiquiátricas, incluyendo depresión, ansiedad, trastorno obsesivo compulsivo y trastornos somatomorfos, ha sido reportada con una mayor prevalencia en el género femenino. Su patogénesis continúa siendo incierta. Algunos factores implicados son la sustancia P, las comorbilidades psiquiátricas y la inflamación perifolicular. Clínicamente se manifiesta con dolor o malestar en el cuero cabelludo, casi siempre en asociación con caída de cabello. La sensación de dolor puede presentarse en todo el cuero cabelludo o de forma localizada en algunas áreas específicas. El diagnóstico es clínico y de exclusión. Respecto al tratamiento, no existen terapias específicas para la tricodinia. Sin embargo, el uso de toxina botulínica A, antidepresivos, neuromoduladores, propranolol, corticosteroides tópicos, corticosteroides orales y cannabinoides tópicos son alternativas terapéuticas a considerar. El tratamiento de la tricodinia continúa siendo un reto terapéutico para el dermatólogo, necesitando más estudios prospectivos para evaluar nuevas terapias.

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Introduction

Trichodynia is the sensation of pain in the scalp associated with certain types of alopecia. Trichodynia manifests or is exacerbated when moving the hair and can sometimes be described as an unpleasant sensation of burning, stinging, or discomfort on the scalp.¹ Although this term was coined by Rebora et al.² in 1996 in patients with diffuse alopecia, it was Sulzberger et al. who first reported on this symptom.³ Initially, trichodynia was associated with telogen effluvium. However, it has now been associated with other types of alopecia.

Epidemiology

Despite being considered a characteristic finding in telogen effluvium, it is a common symptom in androgenetic alopecia. Several studies have reported prevalences of trichodynia in telogen effluvium that go from 40.5% to 73.6% and in androgenetic alopecia that go from 26.4% to 30.2%.^{4,5} Recently, a higher prevalence in scarring alopecias of up to 56.3% was observed.⁶ In the study by Askin et al.,⁶ trichodynia symptoms were found in 27.3% of patients with alopecia areata ($n = 55$), 32% with androgenetic alopecia ($n = 128$), 48% with telogen effluvium ($n = 25$), and 56.3% with scarring alopecia ($n = 32$), without distinguishing between different causes.

Furthermore, it has been associated with other non-scarring alopecias, such as alopecia areata, trichotilomania, and chemotherapy-induced alopecia. Regarding chemotherapy-induced alopecia, Kanti et al.⁷ reported a 100% prevalence of unpleasant sensations or discomfort on the scalp in breast cancer patients on chemotherapy, pruritus and trichodynia in 87%, and only trichodynia in 13% of cases. The most intense trichodynia was reported 18 ± 5

Table 1 Most common diseases associated with trichodynia.

Dermatological	Non-dermatological
Telogen effluvium	Depression
Androgenetic alopecia	Anxiety
Chemotherapy-induced alopecia	Obsessive-compulsive disorder
Scarring alopecias	
Alopecia areata	

days after starting chemotherapy, which corresponds to the onset of anagen effluvium.

Trichodynia has been reported more frequently in women. Prevalence among women is 20%–43.6%. On the other hand, in men, it has been observed in 9%–20.9% of cases.^{7,8} Multiple hypotheses try to explain the higher prevalence of trichodynia in women, some of which include a greater likelihood of seeking medical attention, a higher perception of pain, wearing longer hair, and tying hair up, among others. The coexistence of trichodynia with psychiatric disorders, such as depression, anxiety, and obsessive-compulsive disorder, has been reported as well^{9,10} (Table 1).

Pathogenesis

The etiology is considered multifactorial. Some of the main factors involved include substance P, psychological comorbidities, perifollicular inflammation, and nutritional deficiencies. Substance P represents a crucial element as a mediator of pain perception in nerve endings. It is hypothesized that changes in substance P activity at the perifollicular level could trigger the sensation of pain. Additionally, hair follicles are innervated by nerve plexuses that

produce substance P and other peptides, which play a significant role in regulating the hair growth cycle. Dysregulation in the release of these neuropeptides can trigger hair loss and trichodynia.^{1,8}

Neuropathic pain is another hypothesis in the pathogenesis of trichodynia. Some vitamin or nutritional deficiencies may be associated with neuropathic pain. With current evidence, no relationship has been demonstrated between trichodynia and serum levels of TSH, ferritin, zinc, folic acid, and vitamin B12.^{5,11}

Furthermore, exposure to chemotherapeutic agents is a factor associated with the development of trichodynia. The toxic effect of chemotherapy on scalp blood vessels may be the underlying cause of trichodynia in chemotherapy-induced alopecia. There is a hypothesis about the relationship between the presence of telangiectasias on the scalp and the development of trichodynia. Similar to what has been observed in patients with rosacea, changes at vascular level, such as vasodilation can generate a tingling or burning sensation on the scalp of patients exposed to chemotherapy.⁷

On the other hand, psychiatric diseases are another important factor that should be taken into consideration. A study conducted by Kivanç-Altunay et al.⁴ confirmed a prevalence of psychiatric comorbidities of up to 76% in the group with trichodynia vs 20% in the control group. Among the main associated disorders are depression, anxiety, and obsessive-compulsive disorder.⁴ However, the study by Ozturk et al.¹¹ revealed no greater prevalence of anxiety and depression in patients with trichodynia. An association has been described between an increased expression of neurokinin 1 and nerve growth factor in women with trichodynia, hypothesizing the possibility of these factors in the development of alopecia through nociceptive mediators.¹²

Clinical presentation

Clinically, it manifests as pain or discomfort on the scalp, almost always in association with hair loss. The sensation of pain can occur throughout the scalp or be localized to specific regions. When evaluating a patient with alopecia, it is very important to intentionally inquire about this symptom, as few patients spontaneously report it at the beginning of the consultation.¹⁰ In women, it is common to report pain when moving or brushing hair or tying a ponytail. Furthermore, when wearing longer hair, the weight of hair *per se* can trigger trichodynia, especially among women. The severity, quality, and extent of the symptom can vary. In some patients, the sensation of burning, stinging, or pain predominates, which can significantly impact their quality of life.⁹

Trichodynia, being associated with various causes of hair loss, is usually accompanied by clinical and trichoscopic signs of the underlying alopecia.⁸ In the case of telogen effluvium, there is a positive pull test and hair density loss predominantly bitemporal, along with an identifiable triggering factor. Trichodynia can be a distinctive and prominent finding in severe acute telogen effluvium, with a study by Baldari et al.¹³ finding a significant prevalence of trichodynia in patients with androgenetic alopecia in association with telogen effluvium (34 out of 36 patients). During the

COVID-19 pandemic, a higher incidence rate in the number of telogen effluvium cases was reported. In a series of 128 cases of patients with COVID-19, 66.3% presented telogen effluvium, and 42.4% of these exhibited trichodynia as an accompanying symptom. Furthermore, among those who had trichodynia, there was a higher prevalence of anosmia and ageusia.¹⁴

Another very frequent entity that can present with trichodynia is androgenetic alopecia. In this context, we will find less hair density in androgen-dependent areas in the corresponding topographies in cases of male or female androgenetic alopecia. The pull test turns out usually negative, and trichoscopy highlights the presence of miniaturized hairs, anisotrichosis, a few yellow dots, perifollicular hyperpigmentation, and single-follicle pilosebaceous units.¹⁵

Trichodynia can also occur in alopecia areata, trichotillomania, and chemotherapy-induced alopecia, with clinical and trichoscopic findings of each of these entities leading to a diagnosis of the underlying cause.^{8,9}

Scarring alopecias, such as lichen planopilaris, frontal fibrosing alopecia, folliculitis decalvans, dissecting cellulitis of the scalp, and discoid lupus, are another important cause of trichodynia and pruritus that should be taken into consideration. In each of them, it is necessary to look for the corresponding clinical and trichoscopic findings.⁹

Another possible clinical scenario is the presence of trichodynia without positive clinical or trichoscopic findings for any type of alopecia. In this context, it is necessary to rule out the presence of associated psychiatric comorbidities, mainly anxiety and/or depression.

Diagnosis

The diagnosis of trichodynia is usually one of exclusion and is established through clinical history and complete dermatological examination. It is mandatory to conduct an intentional and extensive interrogation about symptom onset, whether there is any identifiable trigger, its temporality, and accompanying symptoms. Examination and trichoscopic evaluation are essential to identify underlying alopecias. Performing a pull test is a useful test, as it is usually positive in most cases of acute telogen effluvium or alopecia areata incognita. When in diagnostic doubt, a scalp biopsy can be considered, although no trichodynia-related histopathological findings have ever been identified.^{8,16}

Differential diagnosis

The differential diagnosis of trichodynia is mainly with other entities that may present with pain, pruritus, or burning on the scalp, whether accompanied by dermatological signs or not.

Seborrheic dermatitis is among the main dermatological diseases that should be taken into consideration, in which pruritus predominates, along with seborrhea, erythema, and yellowish-white interfollicular scales. On the other hand, contact dermatitis of the scalp may present with burning and/or pruritus, along with erythema and scaling, and associated with a history of a new topical hair care product. Another entity that should be ruled out is lipedematous scalp, in which we will find diffuse pain along

Table 2 Therapeutic alternatives for trichodynia by mechanism of action.

Anti-inflammatory	Antidepressants/ neuromodulators	Substance P inhibitors	Analgesics
Topical or oral corticosteroids 0.5 mg/kg/day (short course) Pimecrolimus cream 10 mg/g	Venlafaxine 37.5–300 mg/day Doxepin 10–20 mg/day	Cannabinoids Capsaicin 0.025%–1%	Propranolol 10 mg/day Low-dose naltrexone 1–5 mg/day
Non-steroidal anti-inflammatory drugs (NSAIDs) Mesotherapy with platelet-rich plasma L-Cystine	Amitriptyline 10–25 mg/day Pregabalin 150–300 mg/day Gabapentin 30 mg/day	Ona-botulinum toxin-A 200 IU	

with paresthesias, with a thickened scalp, accompanied by alopecia. Herpes zoster, presenting with neuropathic pain and paresthesias, is a differential diagnosis that should be taken into consideration, requiring the search for suggestive skin lesions, such as vesicles, erosions, and crusts with a dermatomal distribution, in this case, on the face and scalp. If the patient does not show active dermatological lesions but does have a history of herpes zoster in this topography, consider the possibility of post-herpetic neuralgia as a sequela.^{1,9,16}

On the other hand, in the absence of skin lesions, it is important to rule out temporal arteritis, which generates localized pain, neuropathy, in addition to headache and visual disturbances; or to consider other neurological or psychiatric entities, such as migraine, depression, anxiety, and obsessive-compulsive disorder.^{1,9}

Treatment

The treatment of trichodynia has been little addressed in the literature, and so far, there is no specific treatment algorithm. However, due to the possible pathophysiological mechanisms involved, given its association with various types of alopecias and some psychiatric disorders, we can consider some therapeutic options (Table 2).

Considering the hypothesis of perifollicular inflammation in the development of trichodynia, the use of topical corticosteroids could be beneficial, and their use has been recommended in cases of telogen effluvium.^{9,10} Similarly, although non-steroidal anti-inflammatory drugs could play a role, they have not yet been specifically evaluated in trichodynia.^{9,10} On the other hand, a short 2-week course of oral corticosteroids at a dose of 0.5 mg/kg/day, with progressive tapering, has proven useful in the treatment of hypersensitive scalp.⁹ The use of oral L-cystine supplements has also been described to improve this symptom.¹⁰

Substance P inhibitors can be another useful therapeutic alternative. The use of cannabinoids may be present in some shampoo and hair lotion formulations. Additionally, topical capsaicin 0.025%–1% can initially activate TRPV1, inducing a sensation of pain and burning that progressively reduces with continued use.^{9,10}

Furthermore, onabotulinum toxin-A has been proposed as a treatment based on an isolated experience with a patient with trichodynia refractory to multiple treatments. She was initially treated with 200 IU of botulinum toxin dis-

tributed in 40 points on the scalp, injecting 5 IU per point. After 3 months, she showed a very significant improvement in symptoms, and it was decided to reapply the treatment, resulting in complete resolution of trichodynia and remaining completely asymptomatic at the 9-month follow-up. Within its mechanism of action, botulinum toxin can inhibit the depolarization induced by the release of neuropeptides such as substance P and calcitonin gene-related peptide. By inhibiting these neurotransmitters, pain activation is prevented. In turn, substance P has been associated with hair loss, and botulinum toxin could also be beneficial in the context of trichodynia-related alopecia.¹⁷

Due to its association with psychiatric comorbidities such as depression, anxiety, and obsessive-compulsive disorder, it is important to consider referral to mental health for the identification and treatment of these entities. The use of antidepressants can be beneficial in selected cases. Dual serotonin/norepinephrine reuptake inhibitors such as venlafaxine at doses of 37.5–300 mg/day can be considered. Similarly, antidepressants with antihistaminic function, such as low-dose doxepin (10–20 mg/day) or amitriptyline (10–25 mg/day), have proven effective.

Pregabalin at doses of 150–300 mg/day and gabapentin 300 mg/day are other valid therapeutic options that should be taken into consideration for their neuromodulatory effect.^{9,10}

Low-dose naltrexone has been used in recent years, especially in scarring alopecias. It is an opioid receptor antagonist and has analgesic, anti-inflammatory, and antipruritic effects. Reported doses range from 1 to 5 mg/day in scarring alopecias, especially lichen planopilaris. This drug can be evaluated in trichodynia refractory to other treatments.⁹

Propranolol, a non-selective beta-blocker, has also been used with favorable results. In a 76-year-old woman with treatment-resistant trichodynia and depression as a comorbidity, propranolol 10 mg/day was prescribed for 2 months. Five days into therapy, she showed significant improvement in scalp pain. However, at 6 months, she experienced symptom recurrence upon drug discontinuation and had a new depressive episode.¹⁸

Some studies have shown that patients with trichodynia are more sensitive to touch and pressure in triggering pain.¹ Because of this, it is important to recommend the use of gentle products for the scalp. It is recommended to use fragrance-free shampoos, moisturizing products containing

ceramides or hyaluronic acid and avoid irritating cosmetic products, hot water, and the use of flat irons. Additionally, it is recommended to use hairstyles that do not create tension to avoid triggering an episode of trichodynia. Finally, some relaxation techniques, such as scalp massages, may provide some benefit.^{1,9}

Conclusions

Trichodynia is a very common symptom that occurs both in the context of diffuse alopecia and other entities. It is extremely important to intentionally inquire about this symptom. Its treatment remains a challenge, as there are no specific therapies available to this date. It is essential to assess associated comorbidities to appropriately guide treatment.

Conflicts of interest

None declared.

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