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REVIEW ARTICLE

Drugs and alopecia

Fármacos e alopecia

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Abstract

Drugs are a relatively common cause of diffuse, nonscarring hair loss. They may interfere with the normal hair cycle, either by an abrupt cessation of the mitotic activity of matrix cells, causing anagen effluvium, or by an interruption of the anagen and a premature passage to the telogen phase, originating telogen effluvium. It is essential to obtain a complete history, including previous diseases and medications, focusing on the past 3 months, in order to rule out possible drug-induced alopecia. This review encompasses the most frequently involved drugs, including mechanisms of action and clinical characteristics of drug-induced alopecia. The correct recognition of drug-induced alopecia is essential since the main approach is to stop the offending agent, whenever it is possible.

Keywords: Alopecia. Hair loss. Telogen effluvium. Anagen effluvium. Nonscarring alopecia. Drugs.

Resumo

Os fármacos são uma causa relativamente comum de deflúvio e alopecia difusa, não-cicatricial. Podem interferir com o normal ciclo capilar, quer por uma paragem *abrupta* da atividade mitótica das células da matriz do folículo piloso, originando deflúvio anagénico, quer por uma interrupção da anagénese e uma transição prematura para a telogénese, provocando deflúvio telogénico, e, por vezes, alopecia difusa não-cicatricial. É essencial obter uma história clínica completa, incluindo doenças e fármacos prévios, particularmente nos últimos três meses, de modo a descartar uma possível alopecia induzida por fármacos. Esta revisão engloba os principais fármacos causadores de alopecia, incluindo mecanismos de ação e características clínicas. O correto reconhecimento de alopecia induzida por fármacos é essencial, uma vez que a abordagem principal é suspender o agente imputável, quando possível.

Palavras-chave: alopecia, queda de cabelo, deflúvio telógenico, deflúvio anagénico, alopecia não-cicatricial, fármacos

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Introduction

The hair cycle is composed of three stages: anagen (growth), telogen (resting), and catagen (transition from anagen to telogen). Hair follicle activity varies according to the body region and even in the same area, meaning that each follicle has its own cycle[1]. The normal duration of scalp anagen hairs ranges from 2-6 years, with an average of 3 years. Catagen only lasts 2-3 weeks, followed by telogen, where the follicle remains for 3-6 months. In normal conditions, around 86% of the hairs are in the anagen, 13% in telogen, and 1% in catagen[1]. Many factors, including genetics, the immune system, hormones, or drugs may interfere with the normal hair cycle[2]. Telogen effluvium may lead or not to diffuse alopecia depending on the intensity and duration of the shedding.

Alopecia can be divided into scarring or nonscarring. Drugs interfere with the hair cycle by one of the two mechanisms: an abrupt cessation of mitotic activity of the matrix cells, originating anagen effluvium; or interruption of the anagen phase and induction of a premature passage of the follicle from the growth phase do the resting phase, originating telogen effluvium[3].

Anagen effluvium, due to drugs mainly used in chemotherapy, leads to nonscarring, reversible alopecia[4]. There is a sudden hair loss, since the anagen phase is interrupted, which is observed 1-3 weeks after the initiation of the drug. It usually reverts after 3 months of the drug's cessation[3,4].

Telogen effluvium is the most common type of diffuse hair loss, and it occurs when the hair cycle is interrupted, inducing an abnormal amount of anagen hairs to rapidly enter the telogen phase[3]. The hair loss usually occurs 2-4 months after the administration of the inciting drug (time for a hair follicle to progress through the telogen and be shed)[4]. Techniques such as trichogram, phototrichogram and, rarely, scalp biopsy help to confirm the diagnosis when more than 20% of the hairs are in telogen (although more than 15% is already suggestive), in the absence of inflammation or scarring[3]. Several medications induce telogen effluvium.

Main drugs

Anticoagulants

Different classes of anticoagulants, such as heparin and its derivates[5,6], vitamin K antagonists[7] and, more recently, new oral tyt anticoagulants (NOACs)[8,9] have been reported to induce alopecia. The underlying mechanism is poorly understood. On one hand, it is known that minoxidil increases the secretion of different growth factors, including platelet-derived endothelial cell growth factor[10]. On the other hand, anticoagulation is a recognized cause of platelet aggregation dysfunction, which in turn may also cause a dysfunction of platelet beneficial properties for hair growth[9,11].

Heparin and low-molecular-weight heparins, including enoxaparin and tinzaparin, can cause telogen effluvium, which seems to be more related to the total dose than to the duration of treatment, and reverts with cessation of therapy[5,6]. Vitamin K antagonists, namely warfarin, have been reported to cause reversible alopecia in up to 40% of patients, possibly due to a forced early entry into the telogen phase[7,12].

In 2020, a study comparing different reports of alopecia induced by NOACs with both positive and negative controls (known drugs of causing alopecia or not, respectively), demonstrated a significant over-reporting of alopecia associated with rivaroxaban, apixaban, edoxaban, and dabigatran[9]. Of the four agents, rivaroxaban was the most frequently involved and dabigatran was the least. These differences might be related to their slightly different mechanisms of action. While rivaroxaban binds directly to factor Xa, dabigatran acts through antithrombin III, which is the same mechanism as fondaparinux[12]. This last drug was used as a substitute for rivaroxaban and apixaban in a case of diffuse hair loss with good results[12].

Antihypertensive drugs

Both beta-adrenoceptor antagonists (β-blockers) and angiotensin-converting enzyme (ACE) inhibitors, commonly used to treat hypertension, have been reported to cause alopecia[2].

Keratinocytes contain adrenergic receptors, mainly of the β2 subtype, which are densest at the basal layer and scarcer at the stratum corneum, correlating with keratinocyte differentiation[13]. These may be implied in different adverse cutaneous reactions related to β-blockers, which have been recognized as a cause of alopecia, probably due to a direct toxic effect on the hair follicle[14].

Telogen effluvium has been described after the use of topical timolol in patients with glaucoma, which remitted following drug discontinuation[14,15]. Although it is a topical medication, ophthalmic β-blockers enter the bloodstream through the lacrimal system, increasing their levels in the blood and inducing systemic reactions[15]. A case of patchy alopecia involving the scalp, arms, and chest induced by propranolol was also described. After the withdrawal of the drug, there was complete resolution of the alopecia, which recurred with a re-challenge[16].

Regarding ACE inhibitors, captopril is one of the most implied in inducing diffuse hair loss[2]. The underlying mechanism may be related to zinc deficiency caused by captopril since ACE is a zinc-containing molecule[17]. In fact, zinc supplementation has been reported to reverse the side effects of captopril due to zinc deficiency, such as loss of taste and alopecia[18]. Besides this, a case of alopecia, with normal serum zinc levels, starting 4 months after the beginning of captopril, was reported, suggesting an alternative mechanism[18].

Antimicrobials

Diverse antifungals have been the cause of diffuse hair loss, namely terbinafine[19], fluconazole[20], itraconazole,[21] and albendazole[22].

Terbinafine has been reported to induce acute telogen effluvium, confirmed by trichogram, 3 months after starting the drug, which resolved with its withdrawal[19].

A retrospective study described the occurrence of scalp alopecia in 33 patients medicated with fluconazole[20]. Of note, 88% of these patients were taking high doses (> 400 mg per day) of the drug for the treatment of systemic mycoses, leading to the assumption that this side effect may be dose-related.

Albendazole has been reported to cause anagen effluvium most commonly in long-term or high-dose usage,[23] but the occurrence of alopecia after 2 weeks from the beginning of the treatment has been reported[22]. The underlying mechanism may be related to the antiproliferative effects of albendazole, namely it's capacity to inhibit cellular microtubule polymerization binding to β-tubulin[23].

Isoniazid has also been reported to cause diffuse hair loss 1 month after its initiation for the treatment of tuberculosis[24].

Regarding antiretroviral drugs used for the treatment of human immunodeficiency infection, indinavir has been reported to cause both telogen effluvium and patchy alopecia in up to 10% of the patients[25]. Combination therapy with more than one antiretroviral may be associated with more serious hair loss[4].

Antithyroid drugs

Hypothyroidism is associated with telogen effluvium as well as dry and brittle hair[26]. Along with alopecia areata, patients with chronic telogen effluvium seem to demonstrate a higher prevalence of anti-thyroperoxidase antibodies, compared to the normal population[27].

Hair follicles express thyroid hormone receptors, where both triiodothyronine (T3) and thyroxine (T4) seem to modulate multiple hair follicle functions, including epithelial cell proliferation, apoptosis, and keratin expression[28]. Following this, it is not surprising that overtreatment with antithyroid drugs is a cause of hair loss. However, drugs like carbimazole and thiouracil have been reported to cause telogen effluvium even in euthyroid patients[29].

Anti-tumor necrosis factor alpha (TNF-α) and other biologic agents

Psoriasiform eruption induced by anti-TNF-α agents has an incidence ranging from 1.5 to 5%, but scalp involvement with associated alopecia is usually rare[30,31]. The underlying mechanism might be related to the blocking of TNF receptors, increasing the production of interferon-α by plasmacytoid dendritic cells, which will activate pathogenic T lymphocytes[32]. Most frequently the alopecia presents as inflammatory and nonscarring, although cases of alopecia areata-like and scarring alopecia have been described[33,34]. Histological findings are similar to the ones observed in psoriasis, such as acanthosis with hyper or parakeratosis and a variable number of neutrophils in the epidermis, as well as dermal lymphocytic infiltrate[33]. Occasionally, alterations resembling alopecia areata are also observed, namely an increase in telogen hairs and prominent peribulbar lymphocytic infiltrate[34].

More rarely, cases of psoriasiform alopecia induced by anti-interleukin (IL)—12/23 and anti-IL-17 agents have been reported[35,36]. Clinical and histological features were comparable to those observed in the context of anti-TNF-α therapy.

The suspension of the offending drug is not mandatory and depends on the baseline condition and the severity of the lesions. Psoriasiform alopecia can be managed with topical treatments, such as corticosteroids, calcineurin inhibitors or vitamin D analogs, or systemic therapies, namely cyclosporin or methotrexate[33]. Regarding anti-TNF-α, switching to an alternative agent of the same class may also be helpful[37].

Contraceptives

Hormones play an important role in the progression of the hair cycle, although most of the precise mechanisms behind this modulation still need to be elucidated[38].

Oral contraceptives are implicated in hair loss in two different ways: either due to the androgen activity caused by the progestin component (rare) or to the lack

of mild anti-androgen activity following the interruption of long-term contraceptive therapy (very frequent)[39].

Apart from its interaction with progesterone receptors, progestins also interact with androgen receptors. First-generation (norethisterone) and second-generation (levonorgestrel) progestins show higher affinity to androgen receptors, causing androgenetic alopecia in susceptible women. On the other hand, third-generation progestins (desogestrel, norgestimate, and etonogestrel), drospirenone, and cyproterone acetate have little androgenic or even mild antiandrogenic activity[40]. Progestin implants and intrauterine devices have also been reported to cause alopecia, representing a common cause for the removal of these devices[41,42].

Estrogen, present in combined oral contraceptives, may be responsible for hair growth by extending the anagen phase. This is supported by the fact that after menopause, with the decrease in estrogen levels, women are indeed more prone to develop alopecia[43].

The discontinuation of drugs that prolong the anagen phase, such as oral contraceptives, results in telogen effluvium due to the advance of the follicle into a premature rest[44]. Probably, it is the most common cause of drug-induced alopecia.

Oral contraceptives may have a protective role in the development of frontal fibrosing alopecia, supported by a study with 105 women and 100 controls, where a history of oral contraceptives was significantly greater in the control group[45]. This protection was also verified for intrauterine devices[46].

Cytostatics, immunotherapy, and targeted therapy agents

Alopecia is the most frequent dermatologic side effect of cytostatics, with an estimated incidence of 65%, and it is considered one of the most traumatic aspects of chemotherapy[47].

These agents preferentially target mitotically active cells, inducing cellular stress and subsequent apoptosis. The cells of the hair matrix are among the fastest dividing cells in the human body and therefore are greatly affected by chemotherapeutics, especially if they are in the anagen phase. Catagen and telogen follicles, in contrast, are mitotically quiescent and are relatively spared. As up to 90% of the human scalp is in the anagen phase at a given time, a single dose of chemotherapy can induce widespread follicular damage[48]. It affects mostly scalp hairs because other locations such as eyebrows, eyelashes, axillary and pubic hairs have a lower percentage of anagen hairs[49].

Anagen effluvium is most frequent and severe in patients treated with polychemotherapy, with alkylating agents, antimetabolites, vinca alkaloids, and topoisomerase inhibitors representing the main offenders[50,51]. The degree of hair loss is dependent on the route, dose, and schedule of the chemotherapy and it usually begins 1-3 weeks after the beginning of treatment[52].

Permanent alopecia, lasting more than 6 months after the completion of chemotherapy, has been described as a separate entity[53]. It is more common after high-dose busulfan-containing treatments[54-57], although it can also result from repeated courses of cyclophosphamide and carboplatin or from therapy with taxanes (docetaxel and paclitaxel) for breast cancer[58,59]. Interestingly, a clinicopathological study of patients with permanent diffuse alopecia demonstrated a nonscarring pattern on histologic examination, with an increased number of telogen follicles[47]. This may be explained by both synchronizations of the hair follicle cycling, which follows hair regrowth after anagen effluvium, and a shortening of the hair cycle of follicles that underwent miniaturization. In this setting, a proposed hypothesis for permanent chemotherapy-induced alopecia may be that the drugs precipitate androgenetic alopecia in predisposed individuals. Another theory is the reduction of the stem cells' population in the bulge or papilla[47].

Pharmacological therapies for chemotherapy-induced alopecia include topical and oral minoxidil, although it is not effective in preventing it[60]. This topic will be discussed in more detail in the Management section.

Alopecia areata is part of the frequently described immune-related adverse events, occurring in the context of immunotherapy. Both anti-T-lymphocyte-associated protein 4 (CTLA-4) and anti-cell death protein 1 (PD-1) agents are reported to induce alopecia areata, including the universalis type, in 1-2% of the patients[61,62].

Targeted therapies work by blocking oncogenic pathways implied in cell growth and survival. BRAF and mitogen-activated protein kinase (MEK) inhibitors may frequently induce alopecia, with an incidence of 23.7% for vemurafenib, 18.9% for dabrafenib, and 13.3% for trametinib[63,64]. Both mild diffuse and scarring alopecia have been described with epidermal growth factor receptor inhibitors[65]. The latter has been reported in 5% of patients treated with cetuximab[65], and it can be secondary to folliculitis *decalvans* or erosive pustular dermatosis of the scalp[66,67].

Interferon

Interferon (IFN) related alopecia include telogen effluvium, dystrophic anagen effluvium, alopecia at the injection site, and alopecia areata[68].

A case of dystrophic anagen effluvium confirmed by histopathological examination was reported in a patient treated for hepatitis C virus with pegylated-IFN plus ribavirin, which reverted almost 1 year after stopping the treatment[69].

Multiple cases treated with IFN-α developed patches of alopecia on the scalp, which progressed to alopecia areata universalis. In fact, IFN has been linked to the exacerbation or the occurrence of several types of autoantibodies or autoimmune diseases, including thyroid disorders and insulin-dependent diabetes mellitus, or diseases involving altered cell-mediated immune functions, such as pneumonitis, nephritis, and colitis[68,70].

Telogen effluvium also occurs in up to 50% of the patients, it is not dose-related and regresses with cessation of therapy[4].

Minoxidil

Minoxidil has pro-mitotic effect on hair follicle cells, as well as anti-androgen, anti-inflammatory, and vasodilator properties, inducing the Wnt/β-catenin pathway and affecting the length of the anagen and telogen phases[71]. Withdrawal of topical or systemic minoxidil can, in turn, cause telogen effluvium due to the simultaneous entry of all the follicles, which extended their growth under the effect of the drug, to telogen phase[4]. On the other hand, some patients will have telogen effluvium at the beginning of minoxidil treatment, which may be caused by the induction of the anagen phase on hair follicles with a subsequent detachment of the old club hair[72]. This fact should be carefully explained to the patient.

Psychotropics

Psychotropics, including mood stabilizers and antidepressants, can induce hair loss by affecting the telogen phase of the hair cycle[2].

Lithium causes telogen effluvium in 12-20% of long-term users, along with hair thinning, which can be even more frequent[4,73]. The exact mechanism of hair loss is still unknown, although it can also occur in the context of lithium-induced hypothyroidism. For that reason, thyroid function must be also checked in these patients[2].

Diffuse alopecia arises in up to 8-12% of the patients treated with sodium valproate, in a dose-dependent manner[74]. The underlying mechanism seems to be related to biotin and/or zinc deficiency induced by the drug[75,76]. Although the exact pathogenesis is not entirely understood, oral supplementation with biotin and zinc improves alopecia after 3 months[75].

Telogen effluvium is also common in patients medicated with selective serotonin reuptake inhibitors, especially fluoxetine, but also paroxetine and sertraline to a lesser extent[4,77].

Retinoids

Retinoids function by binding nuclear receptors, which in turn interact with other transcription factors to coordinate gene expression. A study has found that hair loss during systemic therapy with retinoids may be provoked by inhibition of hair shaft formation during anagen and induction of premature catagen, along with significant inhibition of keratinocyte proliferation and a slight stimulation of apoptosis in the matrix of anagen hair bulbs[78].

Isotretinoin and acitretin can induce telogen effluvium with visible alopecia in up to 20% of the patients, which seems to be dose-related[4]. Few cases may be persistent and severe[4,78], or even associated with agranulocytosis, suggesting a common underlying mechanism, such as hair cycle arrest[80]. Fortunately, in this last case, the side effects were reversed with drug withdrawal.

Management

Drug-induced alopecia more frequently involves the scalp and presents as diffuse and nonscarring. In the context of chemotherapy, the occurrence of permanent alopecia is a possibility, but not rule[2].

For a patient with diffuse hair loss, a complete history, including previous diseases, medication, and weight loss, focusing on the previous 3 months, should be taken carefully. Moreover, pull test, trichoscopy, and sometimes (photo) tricogram are valuable techniques that may help differentiate telogen effluvium from other types of alopecia, namely androgenetic alopecia. On the other hand, anagen effluvium is usually easier to diagnose due to the acute and severe onset and the presence of dystrophic hairs on trichoscopy[4]. Further investigation may include complete blood count, thyroid function tests, serum vitamin D, iron profile, or even more specific laboratory parameters according to the patient's history (e.g., serum proteins, vitamin B_{12}, or zinc, if the nutritional deficit is suspected), in order to rule out other causes of diffuse hair loss[39,81].

In drug-induced telogen effluvium, discontinuation of the offending drug will gradually cease hair loss after 2-3 months[4]. The complete recovery of hair volume may take much more time, and this fact should be told to the patients. Nutritional supplements may have a role in promoting hair growth and maintaining its structure[81].

Chemotherapy-induced alopecia may have a slightly different approach. A limited number of effective prevention strategies have been reported, including scalp-cooling techniques, although with variable results and indications[82,83]. Despite the lack of benefit in preventing chemotherapy-induced alopecia, topical and oral minoxidil may help by reducing the time of hair regrowth[48].

Conclusion

In the presence of diffuse hair loss, especially telogen effluvium, a high index of suspicion should be maintained regarding medications, especially if other causes have been excluded. The initial treatment with the responsible drug should be searched 3-4 months before the beginning of the effluvium. In most cases, drug discontinuation will stop shedding in some months. The complete recovery of hair volume will take longer.

This article aims to raise awareness among clinicians of the most frequent drugs involved in diffuse alopecia.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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