Drug-Induced Alopecia

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Abstract

Hair loss is a common complaint, and an understanding of the hair cycle is vital in order to interpret whether hair loss is secondary to medication use, as the use of prescription medications is widespread. When there is a temporal association between the onset of hair loss and the commencement of a medication, the medication is commonly presumed to have caused the hair loss. Drug-induced alopecia is a result of either rapid termination of the normal growth phase (anagen effluvium) or a premature conversion of actively growing hairs into the dormant, resting phase (telogen effluvium). Hair loss, in particular telogen effluvium, may, however, occur in response to a number of triggers including fever, hemorrhage, severe illness, and stress. Because hair loss is often delayed and because diffuse alopecia often begins sub-clinically, it may be challenging to determine the primary of alopecia. As a rule of thumb, adverse drug reactions are reversible provided the causative drug is avoided; however, identifying the culprit medication can be difficult. This chapter will review the normal hair cycle and discuss the major drugs that have been associated with alopecia, along with their mechanism (s) of action.

Keywords

Alopecia • Drug-induced alopecia • Hair loss • Drug-induced hair loss

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Introduction

Hair loss is a common complaint, and an understanding of the hair cycle is vital in order to interpret whether hair loss is secondary to medication use, as the use of prescription medications is widespread. When there is a temporal association between the onset of hair loss and the commencement of a medication, the medications are commonly presumed to cause hair loss. Drug-induced alopecia is a result of either rapid termination of the normal growth phase (anagen effluvium) or a premature conversion of actively growing hairs into the dormant, resting phase (telogen effluvium). Hair loss, in particular telogen effluvium, may, however, occur in response to a number of triggers including fever, hemorrhage, severe illness, and stress. Because hair loss is often delayed and because diffuse alopecia often begins subclinically, it may be challenging to determine the primary cause. As a rule, adverse drug reactions are reversible provided the causative drug is avoided. This chapter will review the normal hair cycle and discuss the major drugs that have been associated with alopecia, along with their mechanisms of action.

Normal Hair Cycle

Imperative to accurately diagnosing hair-related disease processes is a fundamental understanding of the normal hair cycle. Hair on the human scalp grows at a rate of 0.3–0.4 mm/day, corresponding to 1 inch every 2 months or 6 inches per year. Each individual human hair follicle has its own cycle, which consists of three distinct and concurrent phases: anagen, catagen, and telogen, corresponding to growth, involution, and resting phases. The duration of the anagen phase determines the ultimate hair length, with the average duration in normal healthy individuals being 3 years. An understanding of this cycle is vital in order to interpret whether hair loss is secondary to medication use. The anagen, or "active," phase is when hair growth occurs. The cells in the root of the hair divide rapidly, and the longer the hair resides in the anagen phase, the faster and longer it will grow. Approximately 85 % of the hairs on one's head are in the anagen phase at any given time, and this phase can last between 2 and 6 years, the exact timeframe of which is genetically determined.

The hair on the extremities, eyelashes, and eyebrows has an extremely short active growth phase (30–45 days), justifying the short length compared to scalp hair. During this phase, the cells in the papilla divide to produce new hair fibers, and the follicle buries itself into the dermal layer of the skin to nourish the strand. The catagen phase, or "degradation" phase, is a short transitional phase between anagen and telogen. It lasts about 2 weeks and is characterized by follicular shrinkage due to apoptosis. The hair pulls away from its blood and nutrient supply in the dermal papilla, hence pausing growth. About 3 % of all scalp hairs are in this phase at any time. The follicle is 1/6 its original length, causing the hair shaft to be pushed upward. While hair is not growing during this phase, the length of the terminal fibers increases when the follicle pushes them upward. This defines formation of a club hair. During the telogen, or "resting" phase, the follicle is inactive for 1 to 4 months. Telogen typically lasts about 100 days and 6–15 % of the hairs on one's head are in this phase at any given time. The hair follicle is completely at rest and the club hair is fully formed. Pulling a hair out in this phase will reveal a solid, hard, dry, white material at the root. About 100 telogen hairs are shed normally each day. At some point, the follicle will begin re-growth, entering the active phase once again. If the old hair has not already been shed, it will be pushed out by the new emerging hair shaft.

Presentation and Characteristics

Drug-induced hair loss typically presents as a diffuse, non-scarring alopecia of the scalp with rare involvement of other areas such as the eyebrows, axillary hair, pubic hair, and total body hair. Associated symptoms and follicular or interfollicular inflammation are typically absent. Females are more commonly affected than males.

Drug-induced alopecia occurs via two major mechanisms: anagen effluvium and telogen effluvium. Anagen effluvium typically begins within 1–3 weeks of initiation of a new medication and is classically associated with anti-cancer chemotherapeutic agents. The onset of telogen effluvium, however, is delayed for 2–4 months following initiation of a new medication. Both of these conditions cause diffuse, generalized non-scarring alopecia, which are generally reversible following discontinuation of the causative agent. Drug-induced telogen effluvium is usually persistent or progressive while the medication is continued. If a particular drug is suspected, testing involves suspending its use for at least 3 months. Re-growth following discontinuation and recurrence of telogen effluvium upon re-exposure to the medication would support a conclusion of drug-induced alopecia. These two major entities will be discussed in detail below.

Anagen Effluvium

Anagen effluvium is characterized by severe diffuse reversible alopecia, generally in the setting of high-dose chemotherapy. In fact, 65 % of patients undergoing chemotherapy will experience drug-induced alopecia. Anagen effluvium typically affects the scalp most prominently, but terminal hair at other sites, including the eyebrows, eyelashes, axillary hair, and pubic hairs may also be affected. Anagen effluvium most commonly begins 1–3 weeks following initiation of high-dose chemotherapy and becomes most clinically apparent at 1–2 months. It results from direct toxicity of the chemotherapeutic agents to the rapidly dividing cells of the anagen hair matrix. Abrupt cessation of mitotic activity leads to abnormal keratinization of the hair shaft and results in Pohl-Pinkus constrictions (tapering of the hair shaft). When these narrowed areas within the hair shaft reach the surface of the skin, they break off. Telogen hairs are unaffected and thus diffuse, but incomplete hair loss is evident clinically. Within several weeks of drug cessation, the hair matrix resumes its normal activity and complete recovery generally occurs; however, alterations to hair color and texture following re-growth are commonly reported.

Anagen effluvium is most common and severe during combination chemotherapeutic regimens. All cytotoxic chemotherapeutic regimens have been implicated, but it is most common with alkylating agents, antimetabolites, vinca alkaloids, topoisomerase inhibitors, and anthracyclines. Other causes of anagen effluvium may include loose anagen syndrome (caused by a defect in the hair cuticle leading to poorly anchored hairs in young blond girls), syphilis, and exposure to isoniazid, thallium, or boron.

Telogen Effluvium

Telogen effluvium is the most common cause of diffuse hair loss secondary to medication or systemic disease. It is characterized by excess shedding of telogen hairs in the absence of clinical or histological evidence of inflammation. It may, however, be associated with scalp paresthesia or pain referred to as trichodynia. Though scalp hair is most commonly affected, diffuse thinning of pubic and axillary hair may also be noted. A specific and identifiable trigger, such as pregnancy, illness, trauma, malnutrition, or occasionally, initiation of a new medication, generally precedes acute telogen effluvium. Gradual onset and prolonged telogen effluvium may be more difficult to assess and must be differentiated from androgenetic alopecia and chronic idiopathic telogen effluvium.

Though there are several distinct mechanisms by which telogen effluvium can occur, drug-induced telogen effluvium generally occurs via immediate anagen release in which an abnormally large number of follicles are stimulated to leave the normal anagen phase and enter telogen prematurely and simultaneously. Clinically, this translates to increased hair shedding 2–3 months after starting the culpable medication.

There are several clinical tests, which may help to confirm the diagnosis of telogen effluvium. The hair pull test, in which 40–60 strands of hair are grasped firmly between the thumb and forefinger and gently pulled in three separate areas of the scalp, may suggest a diagnosis of telogen effluvium if more than 4–6 (10 %) hairs are released. This test is heavily influenced by

recent shampooing and styling of the hair, so the results may be difficult to interpret and a negative test does not exclude the diagnosis of telogen effluvium. A trichogram, in which a mixture of normal anagen and telogen hairs are forcibly plucked from the scalp, is considered diagnostic of telogen effluvium if more than 20–25 % are telogen hairs.

Telogen effluvium may be precipitated by a variety of metabolic alterations, including fever, severe infection, surgery, thyroid disease, hyperparathyroidism, chronic malnutrition or malabsorptive states, crash dieting with severe protein-caloric restriction, severe hereditary or acquired zinc deficiency, renal dialysis with secondary hypervitaminosis A, allergic contact dermatitis to hair dyes, and severe chronic illnesses such as HIV, syphilis, systemic lupus erythematosus, chronic renal failure, chronic liver failure, and advanced malignancy. Half of hyperthyroid patients and 33 % of hypothyroid patients will have diffuse hair loss, which is reversible upon return to a euthyroid state. Acrodermatitis enteropathica and acquired zinc deficiency due to long-standing parenteral nutrition can lead to severe telogen effluvium, though correction of a subclinical zinc deficiency will not stop the increased shedding of telogen effluvium. Many sources recommend iron supplementation if ferritin levels are below 40 ng/ml in patients with telogen effluvium; however, the relationship between ferritin levels and telogen effluvium remains unclear. At least one study has shown that iron replacement alone does not lead to resolution of hair shedding, but ferritin levels may act as markers of patients' overall nutritional status. Some authors suggest slow onset diffuse hair loss in low iron states may result from temporary failure of follicles to re-enter the anagen phase.

Differential Diagnosis and Work-Up

When a patient presents with a complaint of increased hair shedding or diffuse hair thinning, a thorough clinical history and physical examination is essential. Many patients can recall when the hair loss began and how long it has lasted, though quantifying hair loss can be more difficult. As it is normal to lose between 50 and 150 hairs per day, it may be difficult for patients to truly quantify increased hair shedding. It is important to remind patients that this normal hair shedding occurs during routine washing and styling. Therefore, if an individual is washing and styling every other day as opposed to daily, they may notice more hair loss during these activities and overestimate daily hair loss. In long-haired patients, a subjective clue to hair loss is the amount of times an elastic band is wrapped around a ponytail. A patient may report that this number has increased recently, indicating significant hair loss.

Associated symptoms, such as scalp pruritus, tenderness, inflammation, or scaling should be elicited. A thorough review of systems, including questions regarding recent weight loss, systemic illness or fever, and menstrual history, should be discussed. Heavy periods and amenorrhea can be associated with iron deficiency anemia and endocrine abnormalities, respectively. History of oral contraceptive use, pregnancies, miscarriages, signs of androgen excess and/or polycystic ovaries should be sought. A review of the patient's past medical history for autoimmune disease, hepatic and renal disorders, and chronic infections is indicated. Family history of premature hair loss should be elicited as androgenetic alopecia, which is often hereditary, may fall within the differential diagnosis. Dietary and medication history, including prescription and non-prescription medications, should also be reviewed. Vegetarians/vegans often have increased hair shedding, probably secondary to iron and protein deficiency.

In addition to thorough history, review of systems, and clinical examination, evaluation of a patient with alopecia may include a comprehensive metabolic panel, thyroid panel, hematocrit, ferritin, and ESR. If this workup is negative or the time course is suggestive, drug-induced alopecia should be considered.

Biopsy/Histopathology

Punch biopsy is preferred for evaluation by a dermatopathologist.

- **Telogen effluvium (TE):** Total number of hair follicles is normal with a predominance of telogen follicles, and little to no anagen or catagen follicles. Drug-induced TE induces a

Table 20.1 Differentiating factors: drug-induced vs. idiopathic alopecia

Drug-induced alopecia	Idiopathic alopecia
Temporal association of drug initiation and alopecia	No association with initiation of drug
Cessation of drug leads to recovery and restoration of hairs and reversion of histopathological changes	No recovery of hairs after cessation of drug
No evidence of thyroid dysfunction	± Thyroid dysfunction

shift to the catagen phase, and by the time a biopsy is taken, most follicles are in the telogen phase. Dermal inflammation is absent.

- **Anagen effluvium:** The total number of hair follicles is normal with a predominance of anagen follicles, and little to no catagen or telogen follicles. Dermal inflammation is minimal to absent.
- **Cicatrical alopecia:** Hair follicles and sebaceous glands are replaced by elastic fiber rich-fibrous tissue, which extends above the level of arrector pili insertion (in contrast to normal telogen hairs in which the fibrosis is only in the deeper follicle). Prominent lamellar fibroplasia is typically seen. In early lesions, a moderately dense lymphocytic infiltrate may be seen around the upper 2/3 of the follicle. The epidermis is uninvolved. In later lesions, the epidermis may show some atrophy with loss of the rete ridges.

Differentiating Factors

There are no specific criteria established to diagnose drug-induced alopecia or to distinguish drug-induced alopecia from other causes of alopecia. However, there are several differentiating characteristics that can aid in this distinction (Table 20.1).

Drugs Implicated

Anti-coagulants

Many anti-coagulants are known to cause reversible hair loss, but the exact mechanism and pathogenesis remain unclear. Systemic heparin and heparinoid therapy can cause transitory diffuse hair loss, namely telogen effluvium, in up to 50 % of patients. Animal models have demonstrated that heparin has an anti-mitotic effect on follicular epithelial cells, inhibits anagen growth, stimulates epidermal proliferation, and inhibits epithelial bulb cell proliferation. Hair re-growth characteristically occurs after drug cessation. Low-molecular-weight heparins (LMWHs) are a mixture of short-chain heparins (2,000–10,000 Da) and are safer than unfractionated heparins. Additionally, LMWHs have fewer complications, can be given in discrete doses, and do not require drug monitoring. Dalteparin was the first reported LMWH to cause rapid, diffuse, reversible alopecia. The first report was 10 weeks after dalteparin treatment for sinus thrombosis in a 9-year-old girl and the second case series reported this phenomenon in hemodialysis patients. Hair re-growth commenced nearly 6 weeks after discontinuation of dalteparin. Barnes et al. demonstrated that hair re-growth can be re-established with citrate anticoagulation. Wang et al. reported three cases of alopecia in women after initiation of enoxaparin for central venous and sinus thrombosis. In these cases, telogen effluvium was precipitated by enoxaparin-induced premature transformation of anagen-phase follicles into telogen-phase, resting follicles. Tinzaparin is another LMWH associated with reversible hair loss, which has been documented in a 66-year-old patient on hemodialysis. The effect and severity of LMWH-associated hair loss is thought to be related to the dose and not to the duration of therapy, and

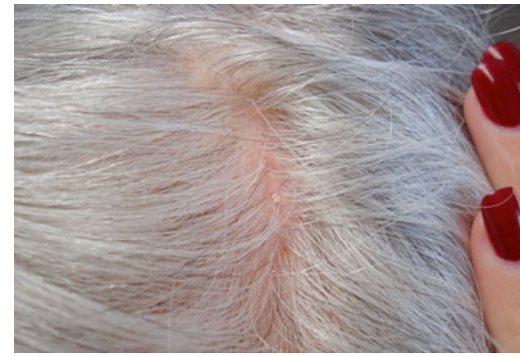

Fig. 20.1 Diffuse hair loss with over 25 % telogen hairs on trichogram that began after Coumadin therapy was initiated. Note the scalp is normal other than mild small non-adherent scaling of seborrhea

there is typically a latent period of 2 weeks from the time of drug administration to hair shedding. Warfarin is less likely to cause clinically significant alopecia, although it has been documented (Fig. 20.1). According to Flesch, the onset of warfarin-induced alopecia may be extremely delayed, often up to years. Three cases of warfarin-induced hair loss were reported by Umlas and Harken, which occurred many years after continuous warfarin therapy for heart disease. They also noted that the alopecia was dose independent and this phenomenon is likely to be under-diagnosed because of the late onset.

Antidepressants

Alopecia is a known side effect of antidepressant medications. Treatment consists of various regimens, including tricyclic or monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRI), or serotonin–norepinephrine reuptake inhibitor (SNRI). Few examples of alopecia induced by tricyclic antidepressants exist in the literature, but cases of hair loss associated with imipramine and desipramine have been reported. No cases of hair loss have been reported with use of MAOIs. Second-generation antidepressants, specifically SSRIs, have caused telogen effluvium. Sertraline, paroxetine, fluoxetine, and citalopram have all been shown to cause reversible alopecia with re-growth as early as 3 months following cessation of use; however, hair regrowth was delayed 1.5 years in a least one case report.

Antimicrobials

Antibiotics, antivirals, antifungals, antihelminthics, and antiretrovirals can all damage hair growth and induce not only telogen effluvium but, rarely, alopecia universalis. Antibiotics have not historically shown a strong predilection toward damaging the hair follicle. Hajime et al. reported a case linking gentamycin to scalp and eyebrow loss following treatment of pseudomonas in a 15-year-old male. Few case reports exist describing dose-related reversible alopecia secondary to nitrofurantoin. The anti-tuberculin drugs isoniazid, thiacetazone, and ethionamide have all been associated with alopecia in the past, but the mechanism is unclear. Hypotheses include involvement of androgen, as isoniazid has been shown to alter estrogen-androgen metabolism. Azole antifungal medications, namely fluconazole and itraconazole, as well as anidulafungin, have been associated with hair loss at high doses. The antihelminthics benzimidazole and albendazole are used for echinococcosis infections, and both have been reported to cause reversible alopecia.

Interferon-alpha (IFN-α), used in the treatment of Hepatitis C, causes dose-independent alopecia in 50 % of patients. Hair loss caused by IFN-α can be localized to an injection site or cause telogen effluvium and, in rare cases, can cause alopecia universalis. The alopecia associated with interferon-alpha therapy is transient and resolves following discontinuation of the drug (see the section on Interferon). Antiretroviral drugs carry a moderate risk for development of alopecia. Approximately 10 % of patients treated with indinavir will experience severe telogen effluvium, possibly with patchy hair loss of the legs, thighs, pubic, and axillary regions. Combined treatment with indinavir and ritonavir may increase the severity of adverse effects because ritonavir increases the plasma concentration of indinavir. A proposed mechanism of action for telogen effluvium associated with indinavir is the enhancement of retinoic acid signaling specific to indinavir. Transitioning to a new drug regimen or discontinuing indinavir will allow restoration of normal hair growth.

Busulfan

Busulfan is a chemotherapeutic agent commonly used in conditioning regimens prior to bone marrow transplant. Unlike most chemotherapeutic agents, which cause a reversible anagen effluvium, busulfan has been reported to cause permanent partial or diffuse hair loss in up to 50 % of patients. Scalp biopsies in these patients demonstrate decreased follicle density without associated inflammation or fibrosis. Reduced follicle density may be a consequence of stem cell destruction or acute damage to matrix keratinocytes.

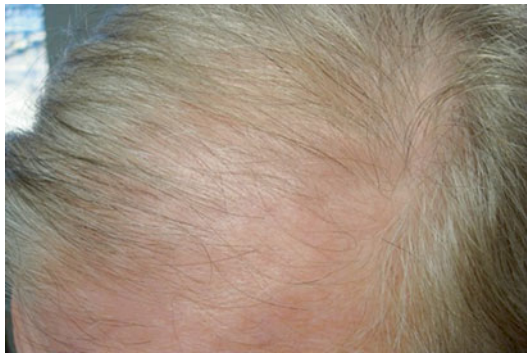

Fig. 20.2 Diffuse hair loss due to a beta blocker, which dissipated months after the drug was discontinued

Cardiovascular Drugs

Beta-blockers are commonly used to treat hypertension, but have a known side effect of alopecia (Fig. 20.2), specifically telogen effluvium. Metoprolol (Lopressor), propranolol (Inderol), and nadolol (Corgard) have been documented to cause telogen effluvium. Hair re-growth has been reported within 3 months of nadolol withdrawal. The angiotensin-converting enzyme inhibitors (ACEi), used in the treatment of hypertension and congestive heart failure, have also been associated with hair loss. In one report a combination of captopril (Capoten) and furosemide cased diffuse hair loss. Angiotensin-converting enzyme inhibitors and β-receptor blocking agents may rarely precipitate a rapidly progressive lichen planopilaris in susceptible patients. Use of these agents in patients with active lichen planopilaris should be avoided. Amiodarone, an anti-arrhythmic, is known for its numerous side effects, including alopecia. In all cases, hair re-growth was reported upon discontinuation of amiodarone.

Chemotherapy Agents

Chemotherapy-induced alopecia (CIA) is commonplace for patients receiving a cytotoxic drug regimen. Although it is a well-known side effect of therapy, the anticipated hair loss can be extremely distressing, enough so that patients consistently rank it among the worst hardships involved with chemotherapy. CIA can be seen within days of initiating treatment, followed by complete hair loss around the second cycle, 4–8 weeks following induction. The degree of hair loss is directly related to dose, schedule, rate, and route of delivery. Hair loss typically begins at the crown of the head, followed by the temporal region. The hair loss can be diffuse or patchy, depending on which individual follicles are in the anagen phase. Chemotherapeutic agents most commonly associated with hair loss include anthracyclines, antibiotics, antimetabolites, vinca alkaloids, and taxanes. The cytotoxic drugs used in chemotherapy target rapidly dividing cells; unfortunately, hair follicles are innocent bystanders and unintended targets. Due to the fact that the hair follicles affected are dividing, or in the anagen phase, the term used to describe CIA is anagen effluvium. It is known that p53 plays a large role in hair follicle apoptosis, and recent studies have shown that Fas and c-kit do play a role, but the exact molecular pathway is still not fully understood. An ongoing debate continues surrounding more hypothetical pathways. The vast majority of patients will have hair re-growth 1-3 months following the discontinuation or completion of chemotherapy, however, the hair texture, thickness, color, and waviness may be altered in up to 60 % of patients.

Dopaminergic Therapy

Levodopa, ergot, and non-ergot alkaloid dopamine receptor agonists have been associated with alopecia and generally affect women more than men. Case reports have documented telogen effluvium in patients with Parkinson's disease that were taking dopaminergic medications. Levodopa, bromocriptine, pramipexole, ropinirole, cabergoline, and pergolide have all been described in the literature as having adverse effects on hair. The pathophysiologic mechanism is unknown, but switching agents or stopping treatment has been shown to reverse the adverse effects over time.

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is a mechanical cardiopulmonary support device that acts as an artificial lung during cardiothoracic surgery or in patients with severe

respiratory distress. Hair loss following EMCO is extremely common and reported extensively. One study demonstrated that up to 87 % of patients will potentially lose hair following utilization of ECMO. The etiology of hair loss with ECMO is most likely multifactorial and resolves spontaneously over time.

Fluoroscopy

Rarely, the use of fluoroscopy during interventional procedures, such as neurointervention following an acute stroke or coronary angiography and angioplasty, has been associated with radiation dermatitis and alopecia in exposed areas. Some authors have termed this "square alopecia," reflecting the geometric distribution pattern frequently observed. This is commonly misdiagnosed as alopecia areata, as the patient may not readily provide a history of exposure to fluoroscopy. It most commonly occurs in the retroauricular region, as the highest dosages of radiation are frequently applied in this location. The severity is proportional to the fluoroscopy dose, the total time of the procedure, the interval between exposures, the size of the irradiated area, and individual patient characteristics, such as age, smoking status, nutritional status, skin integrity, tissue oxygenation, capillary density, hormonal status, genetic factors, obesity, and skin color.

Hormonal Therapies

The estrogen in oral contraceptive pills (OCPs) has been linked to prolonged anagen duration. An alternate hypothesis is that some OCPs contain anti-androgens (drosperidone, cyproterone acetate), which arrest androgenetic alopecia. Subsequent cessation of OCPs presumably then leads to resumption of an unrecognized androgenetic alopecia. Telogen effluvium can also be seen following cessation or interruption of OCPs. Some progesterone-based medications (levonorgestrel, norgestrel, norethisterone, tibolone) may induce or worsen androgenetic alopecia.

Human Epidermal Receptor (HER) Tyrosine Kinase Inhibitors

Tufted hair folliculitis has been reported to develop during treatment with both lapatinib (a HER1 and HER2 tyrosine kinase inhibitor) and trastuzumab (a HER2 monoclonal antibody inhibitor). In the case of trastuzumab, the patient experienced significant scaling and pruritus in association with tufted hair folliculitis. These symptoms resolved with clobetasol propionate 0.05 % topical solution applied twice daily.

The HER1 tyrosine kinase inhibitors erlotinib and gefitinib have been reported to cause a cicatricial alopecia with associated chronic folliculitis and perifolliculitis. Erlotinib has also been reported to cause folliculitis decalvans, which improved with antimicrobial and topical corticosteroid therapy despite continuation of treatment.

Interferon (IFN)

Telogen effluvium occurs in up to 50 % of patients receiving interferon therapy. This effect is not dose-related. Hair shedding is reversible after interruption of treatment and, in some cases, despite continuation of treatment. Changes in hair texture and color upon regrowth are frequently observed. For example, in one report 18 % of patients treated with low-dose IFN-α for malignant melanoma experienced hair whitening. Acquired hair straightening has also occurred in patients on combined IFN-α and ribavirin therapy for hepatitis B. Transient localized alopecia has been reported at IFN-α injection sites.

Multiple cases of localized alopecia areata, alopecia totalis, and alopecia universalis during or shortly after treatment of chronic Hepatitis C with peg-IFN-α and ribavirin have been reported in the literature. At least one case of alopecia totalis involved a patient with pre-existing alopecia areata. Alopecia was noted 3–9 months following treatment initiation, and resolution occurred irrespective of treatment in most patients 3–12 months later. There are at least two reported cases of irreversible alopecia universalis and totalis following peg IFN and ribavirin therapy.

Minoxidil

Topical minoxidil is commonly used in the treatment of alopecia, specifically androgenetic alopecia. Paradoxically, diffuse hair shedding often occurs within 4–6 weeks of initiating therapy secondary to a brief telogen effluvium. Minoxidil

induces premature termination of the telogen phase, leading to simultaneous release of many telogen hairs as responding follicles transition to anagen.

Upon discontinuation of minoxidil, all of the follicles that had prolonged anagen phases during therapy simultaneously enter the telogen phase. This results in a severe telogen effluvium approximately 2–3 months later. Minoxidil has also been reported to induce hair darkening.

Mood Stabilizers

Although uncommon, psychiatric medications can cause alopecia. Mood stabilizers such as lithium and valproic acid are two of the more common inducers of telogen effluvium, but often these symptoms are dose-related and readily reversible with modification of the amount given. It has been reported that 12–19 % of long-term users of lithium will experience hair loss or hair thinning. Alopecia may occur weeks to years into treatment with lithium, with the typical time course being 4–6 months. The adverse drug effects of lithium treatment affect females more often than males. It is essential to rule out lithium-induced thyroid disease, a common side effect of lithium treatment, in patients with hair loss or thinning. Returning the patient to a euthyroid state should readily reverse the hair loss. The incidence of alopecia caused by valproic acid is 0.5–12 %. Valproic acid-associated alopecia seems to be associated with increased valproic acid blood concentration, and dose reduction allows hair regrowth. Carbamazepine therapy can also lead to hair loss, with an incidence of 1.6–6 %. Newer mood-stabilizing compounds such as gabapentin rarely cause alopecia. Among the antipsychotic drug classes, only haldoperidol, olanzapine, and rispiridone have been reported to cause hair loss.

Mycophenolate Mofetil

In a long-term observational prospective study of mycophenolate mofetil use in patients with proliferative lupus nephritis, new onset alopecia was noted in 1 of 33 patients. Due to alopecia being a known complication of systemic lupus erythematosus, these results should be interpreted with caution. As discussed below, alopecia has also been seen in patients taking combination mycophenolate mofetil and tacrolimus therapy for long-term immunosuppression following transplant.

Radiation

Radiation for the treatment of brain tumors commonly leads to cicatricial alopecia in exposed areas of the scalp secondary to permanent destruction of hair follicles. This is most common with radiation doses over 700 Gy. Most patients are not completely bald following therapy, as hair follicles in the telogen phase at the time of the treatment are able to escape destruction.

Retinoids

Retinoids, including acitretin and isotretinoin, which are commonly used in dermatology for the treatment of psoriasis and acne, respectively, are known to cause significant telogen effluvium in up to 20 % of patients. Retinoic acid plays an important role in hair growth, with retinoic acid receptors found throughout every portion of the hair follicle. Tightly regulated control of retinoid metabolism may be required for normal function of hair follicles.

Typically, a dose-related alopecia is most notable on the scalp; however, body hair may also be affected. This side effect appears more often in patients treated with acitretin than isotretinoin. Clinical trials have shown 23 % of patients treated with 50 mg daily of acitretin and 9 % of patients treated with 25 mg daily of acitretin reported significant alopecia versus only 1 % of patients treated with placebo for psoriasis.

Retinoids cause a telogen effluvium primarily due to shortening of the telogen phase with premature detachment of club hairs and diffuse hair shedding. They also cause a decrease in the duration of the anagen phase. An observational study of 30 patients on isotretinoin demonstrated significantly decreased hairs, decreased mean hair density, and decreased numbers of anagen hairs during treatment.

Mild hair loss is also frequently seen in patients taking vitamin supplements containing vitamin A. This effect may be potentiated by concurrent administration of vitamin E. Interestingly,

vitamin A deficiency can also result in alopecia, and topical tretinoin has been successfully used to treat androgenetic alopecia in several studies.

Acitretin-induced full-body poliosis with concurrent alopecia and acquired generalized kinking of the hair (possibly secondary to altered keratinization of the inner root sheath leading to structural changes in the hair shaft), and other acitretin-induced changes in hair color and texture have been reported as well.

Tacrolimus

In a 2005 retrospective study of 59 consecutive simultaneous kidney-pancreas transplant patients, 28.9 % of the patients treated with tacrolimus and mycophenolate mofetil developed clinically significant alopecia, while none of the patients taking cyclosporine with or without mycophenolate mofetil developed alopecia. Females were much more likely than males to experience alopecia.

Alopecia areata and alopecia totalis have also been reported in three females with type 1 diabetes mellitus taking tacrolimus and mycophenolate mofetil following islet cell transplantation. Alopecia was reversible with conventional treatments for alopecia areata, including topical anthralin, salicylic acid, and intralesional cortisone injections, despite continuation of tacrolimus in two of the three cases and continuation of mycophenolate mofetil in two of the three cases. It is important to interpret these reports with caution, however, as alopecia areata is thought to be an autoimmune disease, which may cluster in families with other autoimmune diseases such as type 1 diabetes mellitus.

TNF-α Inhibitor-Induced Psoriasiform Alopecia

TNF-α inhibitors are being increasingly used in the treatment of psoriasis and inflammatory bowel disease. Paradoxically, multiple cases of psoriasiform alopecia of the scalp have been observed in patients with or without a history of psoriasis receiving TNF-α inhibitors, most commonly infliximab and adalimumab. Biopsy of affected areas demonstrates a psoriasiform dermatitis with an increased number of catagen or telogen hairs, miniaturization of hairs, and a peribulbar and superficial perivascular dermatitis with a mixed infiltrate including eosinophils and plasma cells. Cicatricial alopecia may result in protracted cases. Two cases of biopsy-proven lichen planopilaris of the scalp associated with the TNF-α inhibitor, etanercept, including one case in an 8-year-old boy and one case in a 56-year-old woman being treated for severe psoriasis have been reported. A case of lichen planopilaris of the scalp associated with infliximab has also been reported.

Management and Treatment

Iatrogenic hair loss related to medication use has been widely reported in medical literature, with a litany of drugs implicated. Proper evaluation of patients with hair loss is essential to identifying the root cause of the problem. Following a detailed physical examination, review of systems, and laboratory work-up to rule out other etiologies for the hair loss, comprehensive drug reconciliation should be performed. The drug reconciliation should cover all prescription, over-the-counter and chemotherapeutic medications, as well as vitamin supplements, herbal preparations, and adjunctive treatments. Changes in dosage or frequency of intake are to be noted. Since telogen effluvium takes 2–4 months to fully manifest, all medications started within 4 months of initial hair loss must be reviewed. The gold standard for rendering a diagnosis of drug-induced alopecia is discontinuation of the medication in question for an extended amount of time, with subsequent restoration of hair growth.

Following cessation of symptoms and hair regrowth, a second challenge to prove causation should be made if any question remains surrounding the medication's association with alopecia. Identification of the inciting drug and subsequent discontinuation is the cornerstone of treatment in this subset of patients. In a majority of cases for patients with drug-induced telogen effluvium, cessation of the medication will result in a complete recovery, usually within 4–6 months, and rarely with symptoms lasting more

than a year. Patient reassurance is imperative in management, as the concern that they will "go bald" can be overwhelming.

Though telogen effluvium is a self-limited disease, it may exacerbate or precipitate androgenetic alopecia in at-risk patients. In this subset of patients, treatment with topical minoxidil or finasteride may be indicated. As discussed previously, patients treated with chemotherapy may experience anagen effluvium, which is among the most distressing side effects of chemotherapy, potentially affecting body image. The first step in management of these patients is discussion of the anticipated hair loss and exploration of cosmetic options, including wigs, hats, hair cuts, etc.

In patients receiving chemotherapy for non-hematologic malignancies, scalp hypothermia is a proposed method to reduce hair loss. Theoretically, vasoconstriction caused by the low temperature reduces the amount of cytotoxic chemical that reaches the hair follicle. Reduced biochemical activity due to the extreme cold may also deem the hair follicle less susceptible to damage.

As stated previously, the vast majority of patients affected with anagen effluvium will regain their hair within months of cessation of the trigger drug, but it has been shown that patients using topical minoxidil recovered hair approximately 50 days sooner than those using placebo. Patients with telogen and anagen effluvium need a combination of medical intervention along with a healthy support system to fully manage and treat their disease.

Main Points

- Hair loss secondary to medications has been widely reported in medical literature, with numerous drugs implicated.
- An understanding of the hair cycle is vital in order to render a diagnosis of drug-induced alopecia.
- The two main mechanisms by which drug-induced alopecia occurs are anagen effluvium and telogen effluvium.
- Clinical presentation is typically a diffuse, non-scarring alopecia of the scalp, with rare involvement of other areas such as the eyebrows, axillary hair, pubic hair, and total body hair.
- Detailed physical examination, review of systems, laboratory work-up (comprehensive metabolic panel, thyroid panel, hematocrit, ferritin, and ESR), and a thorough drug reconciliation should be performed in all patients presenting with alopecia.
- Most adverse drug reactions are reversible, provided the causative drug is avoided. It can be quite difficult, however, to assign a culprit medication.

Conclusions

Alopecia can have a significant impact on body image. Numerous factors may be implicated, including medications. In most cases, discontinuation of the culprit drug will result in cessation of hair loss and reversal of the process. It is beneficial to identify the drug in question as soon as possible to limit associated psychological damage.

Suggested Reading

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