

## **Inflammation in androgenetic alopecia**

Years of research have led to the conclusion that androgenetic alopecia may be a result of an alteration in the hair growth cycle and/or a premature aging of the pilosebaceous unit. The etiology of androgenetic alopecia has been defined as multifactorial or even polygenic in nature. The fact that the success rate of treatment with either antihypertensive agents or modulators of androgen metabolism barely exceeds 30 percent, has led to some researchers to propose the possibility of other pathways that mediate this form of hair loss.

### **Hair follicle inflammation in androgenetic alopecia**

The new focus, therefore, is the implication of various activators of inflammation in the etiology of androgenetic alopecia. An early study referred to an inflammatory infiltrate of mononuclear cells and lymphocytes in about 50 percent of the scalp samples observed. Jaworsky et al. subsequently in 1992 referred to an inflammatory infiltrate of activated T cells and macrophages in the upper third of the hair follicles, associated with an enlargement of the follicular dermal-sheath composed of collagen bundles (perifollicular fibrosis), in regions of actively progressing alopecia. Whiting has documented that horizontal sections of scalp biopsies indicated that the perifollicular fibrosis is generally mild, consisting of loose, concentric layers of collagen (a fibrous protein that makes up connective tissue) that must be distinguished from cicatricial alopecia. Another study conducted on 412 patients (193 men and 219 women) showed the presence of a significant degree of inflammation and fibrosis in at least 37 percent of androgenetic alopecia cases.

The location of the infiltrate near the infundibulum clearly differentiates androgenetic alopecia from alopecia areata, which is characterized by infiltrates in the bulb and dermal papilla zone. The term 'microinflammation' was proposed by Mahe and colleagues because the process of inflammation in androgenetic alopecia adopts a slow, subtle, painless and lethargic course, in contrast to the inflammatory and destructive process that has been seen in the classical inflammatory scarring alopecias.

The significance of these findings has remained controversial. However, only 55 percent of male pattern androgenetic patients with microinflammation had hair re-growth in response to Minoxidil treatment, which was less than the 77 percent of patients with no signs of inflammation, suggesting that, to some extent, perifollicular microinflammation may account for some cases of male pattern androgenetic alopecia which do not respond to Minoxidil.

### **Inflammatory phenomena in pattern baldness**

An important fact to be established is how the inflammatory reaction pattern in androgenetic alopecia is generated around the individual hair follicle. Inflammation is regarded as a multi-step process which is assigned to a central major mediator or pathway. Mahe et al believe that the presence of a perifollicular infiltrate in the upper follicle near the infundibulum points to the fact that the primary causal event for the triggering of inflammation might occur near the infundibulum.

On the basis of this localization and the microbial colonization of the follicular infundibulum with *Propionibacterium* sp., *Staphylococcus* sp., *Malassezia* sp., or other members of the transient flora, some researchers speculate that that microbial toxins or antigens could be involved in the generation of the inflammatory response. The production of porphyrins (any of various organic compounds containing four pyrrole rings, occurring universally in protoplasm, and functioning as a metal-binding cofactor in hemoglobin) by *Propionibacterium* sp. in the pilosebaceous duct of 58 percent of androgenetic alopecia

patients (compared with 12 percent of control subjects) has also been considered to be a possible cofactor of this initial pro-inflammatory stress.

Alternatively, keratinocytes themselves may respond to chemical stress from irritants, pollutants, and UV irradiation, by producing radical oxygen species and nitric oxide, and by releasing intracellularly stored IL-1a. This pro-inflammatory cytokine by itself has been shown to inhibit the growth of isolated hair follicles in culture. Skin keratinocytes, which may also have antigen-presenting capabilities, could theoretically induce T-cell (white blood cell) proliferation in response to bacterial antigens. These antigens, once they have been “tagged”, are then selectively destroyed by infiltrating macrophages (cells that act as scavengers within the body), Langerhans cells (dendritic cells in the skin that pick up an antigen and transport it to the lymph nodes), or natural killer cells (immune system cells that destroy foreign bodies or abnormal cells that are marked with antibodies).

When any of the causal agents described above persist, it leads to sustained inflammation of the hair follicle. This phase of inflammation often results in tissue remodeling, where collagenases (various enzymes that catalyze the hydrolysis of collagen and gelatin) may play an active role. Collagenases are suspected to contribute to the tissue changes and the so-called “perifollicular fibrosis” by “preparing” tissue matrix and basal membranes for macrophages and T-cell adhesion.

#### Relations between inflammation and steroidogenesis

It has been proven beyond doubt that androgens, in the form of testosterone or its metabolites, are the prerequisites for development of common male pattern baldness. According to Mahe, the only apparent link that can be established between androgen metabolism and the complex inflammatory process proposed by him is sebum production, which is controlled by androgens. As sebum harbors a large amount of microorganisms, which use lipids as nutrients, it is possible that, at least for some individuals, androgen metabolism might make possible the colonization of the sebaceous infundibulum and sebaceous ducts by microorganisms. These microorganisms may well be involved in the first steps of pilosebaceous unit inflammation.

#### Conclusion

Therefore Mahe and his team deduce that the genetic factors and androgen metabolism are only responsible for about 30 percent of the androgenetic alopecia cases, and factors which lead to the lethal damage by microinflammatory process include androgens, microbial flora, endogenous or exogenous stress, genetic imbalance, amongst others. Formation of fibrous tissue or fibroplasia of the dermal sheath, which surrounds the hair follicle, is now suspected to be a common terminal process resulting in the miniaturization. Involution of the pilosebaceous unit in this form of baldness and sustained microscopic follicular inflammation with connective tissue remodeling, eventually resulting in permanent hair loss, is considered a possible cofactor in the complex etiology of androgenetic alopecia. However, till date, the inflammatory component has not been explored in developing treatment protocols for androgenetic alopecia.