

## Alopecia Areata: Why is it Areata?

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Areata is a Latin word that means spotty and applies to alopecia areata (AA) because the disease is most often characterized by one or more bald areas on hairy regions. Although many advances have been made in understanding the pathogenesis of the disease, why alopecia areata is spotty remains unclear and is the object of the present essay.

AA is currently considered an organ-specific autoimmune disease that results from the collapse of the immune privilege of anagen hair follicles and the consequent attack of CD8<sup>+</sup>T cells to the replicating keratinocytes in the hair matrix [1]. Many other autoimmune diseases share the mechanism of the interruption of mitoses in specific cellular targets, but what is peculiar of AA is the particular behavior of the target once it has been attacked by a toxic event, whatever its nature.

In contrast with other epithelial cells in which the response depends only on the intensity of the insult (f.i. the dosage of a drug) and/or its duration, the hair keratinocyte, which undergoes periodic and regular phases of mitotic activity and rest (the hair cycle), responds according to two more conditions: the phase of the hair cycle in which the insult finds the hair follicle, and the presence of conditions capable of modifying the normal length of the cycle phases, most often the coexistence of androgenetic alopecia (AGA). In addition, the mentioned four conditions may also interact (table 1).

Of course, if the insult is very powerful, all the hairs in mitotic activity will be destroyed. The same result is obtained if the duration of the insult is such as to cover all the phases of the hairs cycle and all cycles.

In fact, not all the phases of the cycle are equally susceptible to the insult. The susceptibility of a cell to be destroyed is directly related to its mitotic activity. Telogen hairs, in which the mitotic activity is absent, are spared, representing a sanctuary in which the insulted hair remains for three months before shedding. The insult, instead, produces its maximum effect in the follicles that are in a subphase with a highest mitotic activity (anagen I-IV). In this condition, the follicle undergoes a profound alteration of its structure (dystrophy) and shed as a dystrophic hair. When such an alteration occurs at the outlet of the pilar canal, the pressure exerted by the simple bending of the hair shaft, causes its breaking and what remains of the hair is a black (or white) dot, the so called

cadaverized hair. The follicles, instead, which are insulted when they are close to the end of their anagen phase (anagen V-VI), when the mitotic rate is already spontaneously declining, simply accelerate their normal transition to telogen, and shed as such.

It appears clear, therefore, why alopecia areata is most often patchy. The area will develop only where a group of follicles are simultaneously in the same phase of the cycle in which the mitotic activity in the hair matrix is very high.

Another explanation has been long time ago proposed: the insult produces its maximum effect in an area in which the hair capillaries come from a deeper vascular “cone” that irrigates a circular area. There is no reason to reject this hypothesis, which belongs to the pre-immunology era, simply because the two theories are not mutually exclusive.

This consideration implies other thoughts. The first one concerns the role of a coexistent AGA and its high prevalence in Caucasians. It appears consequential that only people without AGA or with a minor one are susceptible to develop a patchy AA. In fact, the duration of anagen with respect to telogen is crucial for the hair response to the insult. When the anagen/telogen length ratio is low, like in AGA, in which the anagen duration is reduced, the insult is unlikely to find keratinocytes with a high mitotic rate. This explains why AA is rare in people with advanced AGA and in general over 40 years of age, and, vice versa, common in people with a full head of hair.

The second consideration concerns the sites in which the “area” appears. They must be sites in which the duration of the cycle is long enough for the insult to find the susceptible phases with highest mitotic activity. This explains why the involvement of eyebrows, axillae and pubis in which the hair cycle is shorter, bears a bad prognosis. The insult must be very strong to involve such areas. The poor prognosis of ophiasis has probably the same explanation.

The third consideration concerns people who undergo chemotherapy. The insult in this case is toxic (the cytostatic drug), but the response of the hair is the same as in alopecia areata. It is well known that the response to the same cytostatic drug differs in the various patients, and oncologists acknowledge that “several factors may contribute to the severity of hair loss including drug,

dose and schedule” [2]. The local situation of the hair cycles has never been taken into consideration, however. People with a full head of hair would be very likely to shed all their hair, while people with AGA would not.

One may wonder what may happen in people whose scalp hair conditions are not the ideal ones for the “area” to develop. Because of AGA high prevalence, in fact, most Caucasian scalps do not have a “normal” anagen/telogen duration ratio, but one in which the telogen length prevails over the anagen length. In those cases, the usual mode of shedding would therefore be diffuse and telogenic. Whether this mode would correspond to what I use to call autoimmune telogen effluvium (or alopecia areata incognita) remains to be established [3-5].

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