Abstract

Alopecia areata is an autoimmune disease with possible genetic predisposition and trigger causes, with an increasing incidence, especially in children and young adults. It presents several clinical forms, with different severity and prognosis. This article describes widely the clinical forms of alopecia areata, together with their positive and differential diagnosis, evolution and prognosis, and focuses on the latest issues on its etiopathogeny. An exhaustive approach of local and general therapy currently used to treat alopecia areata or to stop its progression is also realized.

Keywords: alopecia areata, autoimmune disease, etiopathogeny and treatment.
Introduction

Alopecia areata presents as patches of hair loss, reversible in most of the cases. It frequently affects children and young adults under 25 years old; men can be affected twice as more as women[(1)]. There are many types of alopecia areata: diffuse alopecia areata - patchy alopecia areata, alopecia ophiasis, alopecia totalis, alopecia universalis. Alopecia ophiasis affects especially children and is localized on the sides and lower back of the scalp. Alopecia totalis (AT) occurs as total hair loss on the scalp and eyebrows. Alopecia universalis (AU) occurs with complete hair loss on the scalp and eyebrows. Alopecia universalis (AU) occurs with complete hair loss on the scalp but any hair-bearing areas can be involved (beard, eyelashes, eyebrows, trunk, arms, legs, axillary region, groin, and other hair-bearing areas) [3].

Clinical presentation

The common clinical presentation of alopecia areata is the appearance of many round or oval alopecic patches, well defined, with a diameter varying between 0,5 – 5 cm. Alopecic patches are normal-colored, glossy, hypotonic, without epidermal change and without scaling and crustling. Alopecia areata usually presents as patches of hair loss on the scalp but any hair-bearing areas can be involved (beard, eyelashes, eyebrows, trunk, arms, legs, axillary region, groin, etc). At the periphery of alopecic patches, the hair can be pulled out easily, without pain. Hair follicles have the characteristic aspect of “exclamation point”. A positive result of the pull test indicates that the disease is active. Depending on the severity of the disease we can find one or several alopecic patches, but the patches can coalesce and affect the entire scalp. The nails are involved in about 10% of patients [5]. One can find some abnormalities of nails like nail pitting, sandpaper nails, Beau lines - transverse striations, trachonychia, koilonychia, dotted leukonychia, etc. [3]. These changes of the nails can appear before, during or after the onset of alopecia areata and can persist for an indefinite period of time. From an etiopathogenetic perspective there are many factors involved:
- immunological factors (alopecia areata is considered an autoimmune disease because of the presence of anti-hair follicle antibodies and of the association with other autoimmune diseases: vitiligo, polyendocrinopathy, drug-induced anagen effluvium, systemic lupus erythematosus, alopecia in secondary syphilis)
- genetic factors (some antigens of the HLA complex seem to favor the appearance of alopecia areata: HLA B8, HLA B9, HLA B12 for diffuse alopecia, HLA DRB-1104 for alopecia areata totalis or universalis and about 20% are family cases) [3].
- psychological factors - stress.
- endocrine factors.

Association between alopecia areata and other autoimmune diseases suggests that alopecia areata is itself an autoimmune disease although this is unproven. It has been proposed that the hair follicle is an immunologically 'privileged tissue' which is sheltered from immune surveillance by autoreactive T cells, and that failure of such immune privilege plays a key role in the pathogenesis of alopecia areata [8, 9].

Differential diagnosis

It is not difficult because alopecia areata is easily distinguished from others alopeciae. Major diseases that are involved in differential diagnosis are: trichotillomania, tinea capitis, telogen effluvium, drug-induced anagen effluvium, systemic lupus erythematosus, alopecia in secondary syphilis. Trichotillomania and traction alopecia present broken hair on alopecic patches and at the periphery of these areas, because of the mechanical factor that contributes to alopecia. Tinea capitis usually presents with alopecic scaly patches, with various dimensions and affects especially the children. Telogen or drug-induced anagen effluvium presents with diffuse alopecia. In secondary syphilis,
serology is always positive (a non treponemal test RPR/VDRL and a treponemal test TPHA/FTA)(3).

Treatment

Since the cause of alopecia areata is unknown, there is virtually no etiological treatment. Alopecia areata therapy may be local and/or general. First-line treatment includes topical application of non-specific irritants (cignoline, phenol), corticosteroids, immunomodulators that produce contact dermatitis (dinitrochlorobenzene -DNCB, diphencyprone - DPCP, squaric acid dibutylester - SADBE, dioxyanthranol-anthralin), vasodilators (minoxidil) and PUVA. In some clinical cases systemic treatment with corticosteroids, cyclosporine or isoprinosine is used(2).

Topical corticosteroids are the first treatment option. Moderately potent corticosteroids are used in most cases of alopecia areata of small or medium severity, but their effectiveness is limited. They are the treatment of choice for alopecia areata in children. The use of topical corticosteroid lotions is preferred because the cosmetic acceptability of this galenic form is superior to a cream or an ointment. The main side effect of these is folliculitis. Two randomized clinical trials on clobetasol propionate 0.05% cream, or ointment have shown its effectiveness in about 20% of patients(5). In a clinical trial of 0.05% clobetasol propionate foam, 34 patients with moderate to severe alopecia areata were randomly assigned to treatment to one side of the scalp and vehicle to the other side. After 12 weeks of treatment, more sites treated with clobetasol versus vehicle had at least 50% regrowth of hair (seven of 34 vs. one of 34)(10). Clobetasol propionate applied under an occlusive dressing may be effective in some patients. In a study of 28 patients who had AT /AU for a mean duration of 7 years 0.05% clobetasol propionate ointment applied under an occlusive plastic film on six out of seven nights for 6 months resulted in longterm hair regrowth in five patients (18%)(11).

Intralesional corticosteroids in low concentrations (2.5 - 5 mg / ml) are a second-line treatment(3). However, in extensive forms of illness in adults intralesional corticosteroids may be the first therapeuetic option. The most used drugs are: diluted triamcinolone acetonide for alopecia areata of the beard, triamcinolone acetonide 5 - 10mg formulation / ml for alopecia areata of the scalp and hydrocortisone acetate (25 mg / ml). Injection of alopecic patches is indicated every 4 - 6 weeks, not to exceed 3 ml / administration. The main side effects include: injection site pain, atrophy of the skin and subcutaneous tissue (can be prevented by limiting the volume injected in one place and avoiding the injection to be too deep or too shallow), the appearance of spider veins, pigmentation changes (hypo- and hyperpigmentation). There is a risk of cataract and raised intraocular pressure if intralesional corticosteroids are used close to the eye, for treating eyebrows(12). There were 2 cases of anaphylaxis following treatment with triamcinolone acetonide(13,14). In a study from Saudi Arabia, 62% of patients achieved full regrowth with monthly injections of triamcinolone acetonide, the response being better in those with fewer than five patches of < 3 cm in diameter(15).

Cignoline is an irritant derived from tar. It is applied to the scalp in low concentrations of 0.5-1%, 2 times a day, and allowed to stay on the skin for 20-60 minutes. The mechanism of action is not well enough understood. Some authors consider that it could act like dinitrochlorobenzene or diphencyprone. The main side effect is severe irritant dermatitis and as inconveniences can be mentioned the unpleasant odor and staining linen(3).

Dinitrochlorobenzene (DNCB) is a strongly immunogenic substance and is used in serial dilutions (in acetone or fat basis) of 0.0001%, 0.001%, 0.01%, 0.1%, 0.5%, 1% and 2 %. The application starts with a concentration of 2% every 1-2 weeks until allergic contact dermatitis occurs. Following induction of the allergic contact dermatitis, dinitrochlorobenzene is applied weekly in small concentrations, so that dermatitis can be kept active for 8-12 weeks. Most patients will develop occipital and/or cervical lymphadenopathy during contact immunotherapy. This is usually temporary but may persist throughout the treatment period(3). Uncommon adverse effects include urticaria(16), and vitiligo(17,18). Its use is limited because there is no
available commercial product, by the severe allergic reaction that it might produce and because of certain fears on its potential mutagenic effect (Ames1 positive test)20.

**Dipencyprone (DPCP)** is an immunogenic substance. The mechanism of action is the induction of an allergic contact dermatitis. It progressively replaced dinitrochlorobenzene because it doesn’t have problematic mutagenicity effects. The absence of a standardized product and the reduced stability of this molecule in pharmaceutical preparations made dipencyprone to be relatively little used21,19.

**Squaric acid dibutylester (SADBE)** is an immunogenic substance like dipencyprone. Topical SADBE represents a valid therapeutic option in severe alopecia areata, and may prove to be disease modifying20.

**Dioxyanthranol-anthralin** (Anaxeryl - dithranol 0.35%) is mixed with a fatty compound and is applied to the affected area, left for 15 minutes, then washed. In one open study, 18% of patients with extensive alopecia areata achieved cosmetically worthwhile hair regrowth20. Since dithranol should be used frequently and in large concentrations in order to obtain an allergic reaction, its use is limited. Out of cosmetic reasons, fair-haired persons cannot use dithranol because it stains the hair.

**Minoxidil** acts on pilosebaceous follicles similar to the “epidermal growth factor”. It seems that it might extend the anagen phase, so it would stimulate DNA synthesis in hair follicles and have a direct effect on keratinocyte proliferation and differentiation. The other effect is the vasodilator one. It is used topically in concentrations of 2% and 5%, 1 ml 2 times/day, associated with topical corticosteroids and/or dioxyanthranol. In terms of cosmetics, treatment is better tolerated than cignoline. In brown women it can give facial hyperpilosity. Topical minoxidil is ineffective in AT/AU.

**Systemic corticosteroids** are used especially in cases of severe alopecia areata, alopecia totalis, alopecia universalis or rapidly progressive alopecia areata. Therapy begins with oral prednisone, which is initial administrated 0.75 mg per kg of weigh daily, then tapered during 6-8 weeks. There are several published case series of high-dose pulsed corticosteroid treatment employing different oral and intravenous regimens (intravenous prednisolone 2 g22, intravenous methylprednisolone 250 mg twice daily for 3 days22,23,24, oral prednisolone 300 mg once monthly25, dexamethasone 5 mg twice weekly26). The results are good and show better hair regrowth at 6 months. It is well-known that most patients relapse when the corticosteroids treatment is stopped. A therapy that appears to be less aggressive is medium-dose pulsed methylprednisolone (100 mg daily, 3 days per month). According to some authors, alopecia areata can be remitted in about 55% of cases (13/23), but the result could not be maintained for a long period of time.

**Photochemotherapy: psoralen plus ultraviolet A** (PUVA). There are 3 types: localized, mixed and generalized. In localized PUVA, psoralen is applied locally followed by irradiation with starting dosage of 0,25J/cm² twice weekly. The dose is increased until the area of treatment is erythematous. The best results are obtained in alopecia of the beard and alopecia ophiasis, where the rate of regrowth is about 100%. In mixed PUVA, oral psoralen and PUVA-therapy are administered on the alopecic patches, but the adverse effects are increased. Regarding generalized PUVA, oral psoralen and PUVA-therapy are administered on the whole body. PUVA is used in extensive and long-term forms of alopecia areata, forms there are resistant to treatment, and in generalized forms. In about 50-65% of cases the therapy was successful. The mechanism of action is linked to the immunosuppressive effect of PUVA on the skin (it reduces the number of Langerhans cells and it interferes with lymphocytes T antigens). The relapse rate following treatment is high. Long-term treatment increases the risk of appearance of skin carcinomas (basal cell carcinoma and squamous cell carcinoma)22.

**Phototherapy with narrow band ultraviolet B (NB-UVB - 311nm)** is used because, unlike PUVA, it has a lower risk of appearance of skin carcinomas. Current data do not allow clear recommendations on the role of UVB in the treatment of alopecia areata23.

**Cyclosporine:** The dual properties of cyclosporine as an immunosuppressive drug and as a hypertrichotic agent make it a logical choice in treating alopecia areata23. Doses of 4-6mg/kg/day have been shown to have a beneficial effect in some patients with alopecia areata. Cyclosporine can be combined with low dose oral prednisone and may be considered in patients with severe atopic dermatitis and alopecia areata24.

**Biological agents** are not proven to be effective. There are several reports of alopecia areata occurring in patients receiving anti-TNF biologic drugs for other conditions25, and in an open-label study in 17 patients with moderate to severe alopecia areata there was no response to treatment with etanercept26.

**Other tested therapies:** sulfasalazine, methotrexate, isoprinosine, laser therapy.
Nonpharmacologic methods: hair transplant, psychotherapy, hypnotherapy, aromatherapy; using of wigs and hairpieces, dermography or semi-permanent tattooed eyebrows.

Figure 5.
Alopecia areata of the beard (personal archive of the authors)

Therapy in special cases of alopecia areata:
- In children topical corticosteroid lotions or ointment can be used. PUVA and immunotherapy cannot be used.
- In pregnant women no treatment is recommended; eventually topical corticosteroid. - Eyelashes alopecia cannot be treated, all that can be done is eyelid tattoo.

Progression of alopecia areata depends of many factors, spontaneous healing appearing in about 60% of cases. The results are much better if the onset of the disease is recent. From the beginning of the treatment the hair still continues to fall for 2 months, because dead hairs are released from pilosebaceous follicles after 60 days, therefore effectiveness of therapy has to be evaluated after this period. Even if the treatment is effective, there is a possibility of relapse at variable time intervals after it is stopped. Evidence in favor of one or another treatment is limited, because there are only few randomized studies, placebo - controlled.

Treatment algorithm
As a conclusion, the general treatment protocol of alopecia areata depends mainly on the age and on the extent of scalp involvement, as follows:
- If the patient is <10 years old, minoxidil 5% solution, topical corticosteroid or short contact anthralin are recommended.
- If the patient is >10 years old and the scalp involvement is <50%, intralesional or topical corticosteroid, minoxidil 5% solution, or short contact anthralin are recommended.
- If the patient is >10 years old and the scalp involvement is >50%, topical immunotherapy (DNCB, DPCC, SADBE) are recommended.
  • For the above patients, if poor response to immunotherapy, minoxidil 5% solution, topical corticosteroid or short contact anthralin are recommended.
  • For the above patients, if good response to immunotherapy, it must be continued.

Bibliography
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