Alopecia Areata: What‘s New?

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Alopecia areata

**Definition:**
Organ specific autoimmune disease of the hair follicle with usually
- rapid
- circumscribed
- non-scarring loss of hair
- variable extent
- unpredictable course
- tendency to recurrence or chronicity.

**Variable clinical presentations and differential diagnosis**

**Co-morbidities and correlations to prognosis**

**Therapeutic algorithm and evolving treatments**
Variability of Clinical Presentation

From: Trüb RM. Haare. Praxis der Trichologie. Steinkopff Darmstadt 2003
Differential Diagnosis: Congenital Universal Atrichia

Rare hereditary atrichia (gene defect on 8p12: human homolog of the mouse hairless gene) in which patients are born with hair that falls out and is not replaced (following the first hair cycle).

Biopsy reveals very few hair follicles which are dilated and without hairs, absence of inflammatory infiltrate, and small keratinous cysts (atrichia with horn cysts)

Clinical examination reveals almost complete absence of hair and numerous papular lesions in the face, on ellbows, and knesse (atrichia with papular lesions)

Marie Antoinette Syndrome

Phenomenon of turning white overnight

Thomas More Syndrome

Phenomenon of turning white overnight in a male patient

Why Henry of Navarre’s Hair Could Not Turn White Overnight

Navarini AA, Trüeb RM. Why Henry III of Navarre’s Hair probably did not turn white overnight. Int J Trichology 2010;2:2-4

St. Bartholomew’s Night Massacre
August 23, 1572

Poliosis in alopecia areata
Acute Diffuse and Total Alopecia of the Female Scalp

Described in Asian women

Predominantly females > 40 years

Favorable prognosis

2% of cases of alopecia areata

Basically identical with:
• **diffuse alopecia areata** proposed in 1962 by Braun-Falco and Zaun in the German literature

• **Alopecia areata incognita** proposed in 1987 by Rebora

Dermatoscope Diagnostic Tool in Alopecia Areata Incognita

Telogen effluvium

Alopecia areata

Androgenetic alopecia

Pathobiology: Organ Specific Autoimmune Disease

**Histopathology:**
- Peribulbar lymphohistiocytic infiltrate („bee swarm“)

**Immune genetic associations:**
- HLA haplotypes
- Cytokine gene polymorphisms
- Susceptibility genes
- Severity genes

**Association with circulating autoantibodies:**
- Thyroid
- Parietal cell
- Hair specific antigens

**Association with other autoimmune diseases**

**Response to immunomodulatory therapies:**
- Corticosteroids
- Cyclosporin
- Methotrexate
- Topical immunotherapy with DNBC, DCP, SADBE

Co-Morbidities

Other autoimmune diseases:
- Autoimmune thyroid disease (7-27%)
- Chronic atrophic gastritis with Vit. B12 deficiency
- Vitiligo
- Autoimmune polyendocrinopathy
- Lupus erythematosus

Low serum ferritin levels: Levels of serum ferritin
- Androgenetic alopecia 37.3 ng/ml
- Multilocular alopecia areata 24.9 ng/ml
- Alopecia areata totalis 52.3 ng/ml
- Telogen effluvium 50.1 ng/ml
- Normal controls 59.5 ng/ml

Kantor et al. Decreased serum ferritin is associated with alopecia in women. J Invest Dermatol 2003;121:985-8

Psychopathologic disorders:
- Trichotillomania

Trüeb und Cavegn. Trichotillomania in connection with alopecia areata. Cutis 1996;58:67-70

- Adjustment disorders
Autoimmune Polyendocrinopathy Syndrome (Type I)

Currently single known monogenetic autoimmune disease (AR, mutation of the AIRE- or autoimmune-regulator gene):

**Major clinical symptoms:**
- Addison’s disease
- Hypoparathyroidism
- Chronic mucocutaneous candidiasis

**Additional features:**
- Type I diabetes
- Autoimmune thyroid disease
- Pernicious anemia
- Hypergonadotrophic hypogonadism
- Alopecia (areata)
- Vitiligo

Alopecia universalis has been described both in association with HIV infection and in the setting of immune restoration after highly active antiretroviral therapy.


Alopecia Universalis Elicited During Treatment with Anti-TNFα

Single case reports and small case series of alopecia areata elicited during treatment with infliximab and other anti-TNFα therapies

“17 trials ... with a total of 540 participants. Each trial included 6-85 participants and assessed a range of interventions that included: topical and oral corticosteroids, topical ciclosporin, photodynamic therapy, topical minoxidil. None showed significant treatment benefit in terms of hair growth when compared with placebo.“

“Few treatments have been well evaluated in randomised trials. We found no RCTs on the use of DCP, DNCB, intralalexional corticosteroids or dithranol, although commonly used. Although topical steroids and minoxidil are widely prescribed and appear to be safe, there is no convincing evidence that they are beneficial in the long-term. Most trials have been reported poorly and are so small that any important clinical benefits are inconclusive.

“Considering the possibility of spontaneous remission especially for those in the early stages of the disease, the options of not being treated therapeutically or, depending on individual preference wearing a wig may be alternative ways of dealing with this condition.“

Prognosis

Spontaneous remission of initial attacks:
• 1/3 within 6 months
• 1/2 within 12 months
• 2/3 within 5 years, thereafter total remission rare.

Recurrence rates:
• 80% within 5 years
• 100% within 20 years

Prognosis of Alopecia totalis/universalis with duration > 5 years:
• Remission in 1% of children
• Remission in 10% of adults
Negative Prognostic Factors

Onset at young age (before puberty)

Longstanding disease

Ophiasis

Alopecia totalis, Alopecia universalis

Nail changes

Association with atopic dermatitis (frequent)

Association with autoimmune polyendocrinopathy (rare)
Nail Changes in Alopecia Areata


Ajith et al. Efficacy and safety of the topical sensitizer squaric acid dibutyl ester in Alopecia areata and factors influencing the outcome. J Drugs Dermatol. 2006;5:262-6
Any treatment of alopecia areata should fulfill the following criteria:

- **Remission rates superior** to spontaneous remission rates of alopecia areata

- **Proof of efficacy in half side treatment** of alopecia totalis or universalis

- **Good safety profile** with minimal toxicity

Depending on patient age, surface area, and disease duration a treatment algorithm can be designed.
ALOPECIA AREATA

AGE

< 10 years

> 10 years

% Surface area

< 30%

> 30%

No therapy or placebo therapy:
• 1% Topical hydrocortisone
• Topical mometasone
• Anthraline
• Oral zinc gluconate

No success

Intralesional triamcinolone acetonide:
• Children: 5 mg/ml
• Adults: 10 mg/ml
• Eyebrows: 2.5 – 5 mg/ml

± Topical minoxidil
± Oral zinc gluconate

No success

Disease duration

< 6 months

> 6 months

Optional: Topical clobetasol propionate (under occlusion)

Steroid pulse therapy
• Oral minipuls therapy
• I.V. methylprednisolone

DCP or SADBE or Methotrexate
± Prednisone

No success

Concomitant:
• Treat disease modifying comorbidities:
  - iron deficiency
  - zinc deficiency
  - vitamin B12 deficiency
  - thyroid disease
  - emotional distress
• Hypnotherapy
• Hair replacement (hair piece, wig)
• Hair coaching/self help organizations

Treat disease modifying comorbidities:
• iron deficiency
• zinc deficiency
• vitamin B12 deficiency
• thyroid disease
• emotional distress

Hypnotherapy
Hair replacement (hair piece, wig)
Hair coaching/self help organizations
Corticosteroid Pulse Therapy

**Methylprednisolone pulse therapy:**
500 mg i.v. for 3 consecutive days, 3x with an interval of 4 weeks

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<thead>
<tr>
<th>Alopecia areata duration &lt; 6 months:</th>
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<tr>
<td>&lt; 50% surface:</td>
<td>88.0% success</td>
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<td>&gt; 50% surface:</td>
<td>59.4% success</td>
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<tr>
<td>Total alopecia:</td>
<td>21.4% success</td>
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<th>Duration &gt; 6 months: 15.8% success</th>
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**Oral minipulse therapy:**
5 mg betamethasone on 2 consecutive days per week for 12 - 24 weeks


In comparison, **i.v. methylprednisolone pulse therapy with highest efficacy**

Half Side Treatment: Topical Corticosteroids

28 patients with alopecia totalis/universalis > 1 year duration

Daily **Clobetasol propionate 0.5% ointment under occlusion on 6 consecutive days per week** during 6 months

8/28 (28.5%) regrowth of hair within **6-14 weeks**

In 3/8 recurrence within 12 months

**Total success rate: 17.8% (5/28)**

**Negativ prognostic factors:**
- positive family history for alopecia areata
- Disease onset before age of 10
- Atopy
- Autoimmune thyroid disease

Side effects: folliculitis/acne in 12/28


Tosti A et al. Efficacy and safety of a **new clobetasol propionate 0.05% foam** in alopecia areata: a randomized, double-blind placebo-controlled trial. J Eur Acad Dermatol Venereol 2006;20:1243-7

![Image of before and after hair growth]
Half Side Treatment: Topical Immunotherapy (DCP)


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<tr>
<th>Remission rate:</th>
<th>Non</th>
<th>Partial</th>
<th>Total</th>
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<td>AA multilocularis</td>
<td>12.5%</td>
<td>43.8%</td>
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<td>AA subtotalis, Ophiasis</td>
<td>20.8%</td>
<td>45.8%</td>
<td>33.3%</td>
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<tr>
<td>AA totalis/universalis</td>
<td>46.4%</td>
<td>32.1%</td>
<td>21.4%</td>
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Total success rate: 30.9%
Methotrexate (and Prednisone)

22 patients with AA totalis/universalis > 1 year

MTX 15 - max. 30 mg/week for max. 18 months after regrowth of hair
+ Prednisone 20 mg until regrowth of hair, thereafter tapered over 6-12 months

Total remission rate 64% (16/22):
68% (11/16) combined therapy
50% (3/6) Mtx (≥ 20 mg) alone

Regrowth of hair within 3-6 months:
Combined therapy 2-4 months
Mtx alone 5-7 months

Psychotherapy

Adjustment disorders frequent:
• with depressed mood (F43.20)
• with anxiety (F43.28)
• with disturbance of conduct (F43.24)

Positive effect of concomitant antidepressive therapy:


Successful Treatment of Alopecia Areata

F, 66-years old, diffuse alopecia areata, methylprednisolone pulse therapy, 3 x 500 mg i.v. on 3 consecutive days, 3 times on monthly basis

F, 21-years old, mutilocular alopecia areata, 3 months combination of intralesional triamcinolone acetonide 10 mg/ml and 5% topical minoxidil 0.2% triamcinolone acetonide twice daily

M, 38-years old, 6 month clobetasol propionate under occlusion overnight 6 days/week

F, 12-years old, subtotal alopecia areata (ophiasis), 12 months DCP therapy (1.0%)

F, 43-years old, total alopecia (areata), 18 months, initially methotrexate 30 mg weekly and prednisone 20 mg daily, tapered to methotrexate 15 mg weekly and prednisone 5 mg daily

F, 47-years old, autosuggestion therapy/visualization exercises, 12 months

Hair Transplantation and Dermatography (Permanent Make Up)


Evolving Therapies for Alopecia Areata

New drug treatment opportunities based on the results of a genome-wide association study, which implicate T cell and natural killer (NK)-cell activation pathways, are leading to new approaches in future clinical trials of alopecia areata.

Special attention is being given to the UL 16-binding protein (ULBP3) gene cluster on chromosome 6q25, as these genes make the NKG2D-activating ligand or signal that can trigger the NKG2D receptor, initiating an autoimmune response.

A greater expression of ULBP3 has been found in hair follicles in scalp biopsy specimens from patients with active disease. It is now postulated that the characteristic T cell "swarm of bees" infiltrate seen in alopecia areata is the result of T cells being attracted to the hair follicle by NKG2D-activating ligands.

**Complexity in pathogenesis may be an opportunity in terms of targeting the disease therapeutically:**

Future treatment approaches for alopecia areata include use of drugs that:

(i) block the NKGD-activating ligand and NKG2D receptor interaction,
(ii) halt activated T cells, or
(iii) modify the inflammatory cytokine network.

**Drugs currently being used or being evaluated for other autoimmune diseases that work through these mechanisms might prove to be very effective in alopecia areata:**

- CTLA4-Ig fusion protein (Abatacept) blocks co-stimulation of T-cells
- anti-IL15Rβ mab blocks activation of CD8+ T-cells
- (Janus Kinase) JAK3-inhibitor (Tofacitinib) blocks signal transduction (IL-15R)
- JAK1/2-inhibitor (Ruxolitinib) blocks signal transduction (IL-15R)
Thank you for your attention!