How to provide an effective evaluation without losing your mind or staying until midnight

Rule 1
Define goals of today’s visit
Steps needed to reach diagnosis
Rule outs
Therapy

Rule 2
Use questionnaires, overprinted exam form / template, videos, handouts

Rule 3
Must do’s during a first visit
  Trichodystrophy
  Telogen or anagen effluvium
  Is biopsy needed?
  Is blood work needed

**Types of telogen effluvium**
Early anagen release
  Febrile illness, diet
Delayed anagen release
  Pregnancy
Early telogen release
  Minoxidil
Delayed telogen release
  Seasonal, pregnancy
Short cycle
  Pattern

**Anagen effluvium**
Chemotherapy
Alopecia areata
Lues
Heavy metal ingestion
**Indications for Biopsy**

- Scarring alopecia
- Non-responsive “AA”
  - Lupus
  - Metastatic breast carcinoma
- Diffuse alopecia areata
- Moth-eaten alopecia (serology -)
- Trichotilllosis

**Where to Biopsy**

- Active lesion
  - Erythema, induration
- Established lesion of LE
  - At least 4 month old
- Burnt-out scar
  - Elastic stain for diagnosis and potential for regrowth

**Maximize Yield of Biopsy**

- Two 4 mm punches
- Parallel to direction of hair growth
- One bisected transversely
- One bisected vertically
- Tell the lab what you are doing
- One transversely bisected punch, ½ vertically bisected punch
- Embed all pieces in one cassette, cut side down

**Increased shed, diffuse**

- Trichodystrophy
  - No labs
- Tapered fractures
  - RPR
- Anagen effluvium
  - No labs
- Telogen effluvium
  - Obvious cause: no labs
  - No obvious cause:
    - Fe, TIBC, saturation, ferritin
    - TSH
    - (ANA, ESR, RPR)

**Increased shed, patchy**

- Trichodystrophy
No labs
Tapered fractures
RPR
Telogen
No labs
Papulosquamous, LE

**Chronic diffuse or pattern**
Tapered fractures
RPR
Usually no increased shed
- Look for reversible causes of low grade telogen effluvium
- Iron studies
- TSH

**Virilization**
Labs as for hirsutism

**BIOPSY TECHNIQUE**

A 4 mm biopsy punch is placed parallel to the direction of hair growth. (In the case of a curly haired patient, the punch is placed perpendicular to the skin surface). The punch is rotated down to the fat, and the 4 mm cylinder of tissue is removed.

**VERTICAL VS. TRANSVERSE SECTIONS**

*Vertical sections demonstrate fewer hairs* than transverse sections. Vertical sections can provide useful clues not generally seen in transverse sections, especially *changes at the DEJ and SQ fat.*

*Transverse sections demonstrate 20 - 30 hair follicles in a single section.* *Anagen/telogen ratios and assessment of miniaturization of hair shafts* are easy in transverse sections.

There are advantages to each method. A blinded study demonstrated that a combination of vertical and transverse sections was superior to either alone. When only one method was used, vertical sections were superior overall, but this may relate to a high proportion of scarring alopecia cases included in the series. For non-scarring alopecia (especially pattern alopecia and telogen effluvium) there are more advantages to using transverse sections. A surprising finding was that serial vertical sections were superior for the diagnosis of alopecia areata (a form of non-scarring alopecia).

My recommendations:
- Whenever possible, I recommend two 4 mm punch biopsies. The first is bisected vertically. Half is submitted for vertical histological sections. The other half can be sent for direct immunofluorescence.
The second 4 mm punch biopsy specimen is bisected transversely through the dermis, about 1 mm above the dermal / SQ junction. Both halves are submitted for histological sections.

The clinician must alert the lab that the bottle contains alopecia specimens requiring special handling. Labels can be attached to the specimen container that read:

“Three fragments of tissue (half of a vertically bisected punch and both halves of a transversely bisected punch.”

To help the lab technicians orient the specimens, the clinician can ink the cut side of each fragment, then simply tell the lab techs to embed each piece "inked side down."

Elastic tissue staining

Elastic tissue stains demonstrate the presence or absence of true scarring. Hyalinized dermis (as in morphea) will still demonstrate intact elastic fibers. Fibrous tracts are easily identified by the surrounding sheath of elastic fibers.

When elastic fibers are disrupted, they recoil like stretched rubber bands that have been snipped. They will appear thick in the areas adjacent to a true scar.

Discoid lupus erythematosus produces scarring throughout the dermis. Lichen planopilaris results in superficial wedge-shaped scars, as does folliculitis decalvans. Morphea produces hyalinization of the dermis without true scarring.

PAS

Thickened basement membrane zone, apoptotic cells and fungal elements are highlighted by PAS staining.

NORMAL HAIR CYCLE

Normally, more than 80% of scalp hairs are growing anagen hairs. Less than 20% are resting telogen hairs. Only a small percentage of hairs are catagen hairs.

As the anagen hair follicle enters catagen, the volume of the outer root sheath decreases by apoptosis of cells. The base of the shrinking catagen follicle moves upward, so that the final resting telogen follicle has no outer root sheath below the level of the sebaceous duct. Below this point, the fibrous tract marks the path of retreat of the catagen hair. The fibrous tract represents the collapsed fibrous sheath of the anagen hair.

Anagen follicles have an inner root sheath. Catagen follicles have apoptotic cells in the outer root sheath. Telogen follicles have club hairs with no inner root sheath. Vellus hairs are miniaturized. The hair shaft is smaller than 0.03 mm and is thinner than the inner root sheath.

In transverse sections, follicles are arranged in follicular units. Each unit is composed of 2-4 terminal hairs and one vellus hair. The transverse area of a 4 mm punch biopsy is about 13 mm². Hair density can be calculated by dividing the number of terminal hairs by 13. A density of about one follicular unit (each with 2 - 4 terminal hairs) per mm² is normal.

Anagen hair counts are usually done at the level of the isthmus (between the erector pili insertion and the sebaceous duct). At this level anagen hairs demonstrate a keratinizing inner root
sheath. Above the level of the sebaceous duct, anagen counts become inaccurate, because the inner root sheath has been shed. The level of entry of the sebaceous duct is easily identified by the wavy eosinophilic cuticle which lines the follicle at this level.

BASIC APPROACH TO SCALP BIOPSIES

1) Is there and objective decrease in the number of hair follicles?
2) Is there alteration of the anagen/telogen ratio?
3) Is there miniaturization of hair shafts/follicles?
4) Is there inflammation?
5) Where is the inflammation?
6) What inflammatory cell types are present?
7) Is there scarring? (Elastic tissue stain)
9) Is there interface change?
10) Is there dermal mucin?
11) Is there pigment incontinence?
   (Below the DEJ? Within fibrous tracts?)
12) Are there empty follicles, pigment casts, catagen hairs or trichomalacia?
13) Are hair fiber granulomas present. Any process which destroys follicular epithelium will result in exposed hair fibers with foreign body granulomas.

Hirsutism

Familial, Long-standing
No labs
Laser
Wax
Bleach
Shave
Chemical depilatories
Spironolactone, OCP

Post-menopausal, mild -moderate
No labs
Replace Estrogen (SHBG)
Decreased Provera
Epilation

Severe, new, progressive
HCG, FBS, Lipids, TSH
Assays for Testosterone are highly lab dependent
History and Physical: Better predictive value than Testosterone and DHEA-S

Androgens
About half from adrenal glands
About half from ovaries
   Theca cells and peripheral conversion

SHBG
Increased by estrogens and thyroid hormone
Decreased by androgen excess, obesity, GH excess

Virilizing tumor
History/physical exam
Total testosterone > 200 ng/dl
DHEA-S > 8000 ng/dl
Imaging studies (U/S, CT, MRI)

Non-classic 21-hydroxylase Deficiency
Homozygous recessive
Up to 10% of our patients with severe hirsutism
Screening:
   baseline AM 17-OH-progesterone (follicular phase, progesterone)
   Stimulated 17-OH-progesterone
Outcome with HS dexamethasone may be no better than empiric treatment with spironolactone

PCOS
Most of our patients with severe hirsutism
Ovarian theca cells produce androgens
Muscle and adipose resistant to insulin
Ovaries not resistant
Abnormal GnRH regulation
Secondary dysregulation of LH

PCOS
NIH Consensus Conference definition
Chronic anovulation (< 9/yr or cycle > 40d)
Clinical signs of androgen excess
Exclusion of other causes

**PCOS**
LH/FSH ratio elevated in only 50%
Cysts on ultrasound not a requirement
Hyperprolactinemia up to 30%
Testosterone normal to increased
SHBG low (obesity)
Hyperlipidemia
Hirsutism, acne, alopecia
Obesity
Abnormal menses
Often history of early puberty
Onset during puberty

**PCOS**
Androgens converted to estrogen
  Risk of endometrial cancer

**PCOS Management**
Hair removal / antiandrogens
Protect endometrium
  OCP +/- insulin sensitizer
Hyperlipidemia
Screen for DM and HTN
  FBS and 2 hr Glucose Tol. test

**Hirsutism in PCOS**
Treatment
  Mechanical / laser /galvanic epilation
  Spironolactone 100 mg BID
  OCP
Insulin sensitizers (Biguanides, Thiazoladinediones)

**OCP**
Estrogen increases SHBG
Progestin inhibits gonadotropin secretion
  Desogestrel, gestodine, norgestimate less adrogenic
  Levonorgestrel, cyproterone acetate
  Metformin (Glucophage)
  Troglitazone (Rezulin)
Hirsutism
Other agents
Rosiglitazone (Avandia)
Pioglitazone (Actos)
Flutamide
Metformin
Cyproterone acetate
Luprolide plus estrogen
Finasteride

Future
Spironolactone plus insulin sensitizer
+/- OCP
+/- newer and better antiandrogens or 5-alpha-reductase inhibitors

References:


