

Female Androgenetic (?) Alopecia

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It is nearly 100 years since the publication of Dorothy Osborn's paper on the inheritance of common balding.¹ From a study of 22 families, she concluded that balding is due to a single gene and is inherited as an autosomal dominant trait in men and autosomal recessive in women. Two twin studies, one in young men and the other in elderly men, have confirmed the importance of genetics in male balding showing heritability in the region of 80-95%,^{2,3} although the single gene idea has now been supplanted by a polygenic model. Initial case control studies found an association between male AGA and polymorphisms within the androgen receptor gene on the X chromosome.⁴ The presence of a major AGA locus within the androgen receptor/ectodysplasin A2 receptor region has been confirmed in subsequent genome wide association studies (GWAS)⁵ and these studies have gone on to identify a further 11 loci scattered across the genome that also show association with male AGA.⁶⁻⁸ The functional significance of these loci is not yet known but may include the regulation of androgen responses and participation in WNT signaling.

What about female AGA? The application of the term "androgenetic" to female hair loss has implied an identity with male AGA, but it has also colored our thinking—because we have given it the same name it must be the same condition. Is this really true? There are certainly similarities; like male AGA the female form is common

and increases in prevalence and severity in the population with advancing age, and the histopathology of male and female AGA is essentially indistinguishable. Androgens are clearly required for the expression of male AGA and there is little doubt that hyperandrogenism in women, particularly when severe, is associated with scalp hair loss. Hamilton refers to reports of such cases in his seminal publication on the role of testosterone in causing male AGA.⁹ On the other hand, many women with AGA have no other clinical or biochemical signs of hyperandrogenism and female AGA has been reported in the absence of circulating androgens and in androgen insensitivity syndrome.^{10,11} A recent questionnaire study in women being treated with testosterone implants for androgen deficiency actually reported an improvement in hair growth in those complaining of hair thinning prior to treatment.¹² Antiandrogens have been widely used to treat female AGA but the quality of evidence for efficacy is poor. Of the better studies, a randomized clinical trial (RCT) of finasteride 1mg daily in postmenopausal women with AGA failed to show any benefit after a year of treatment.¹³ A 1-year trial comparing topical minoxidil with cyproterone acetate (CPA) reported improvement in the minoxidil group but overall deterioration in those receiving CPA.¹⁴ Sub-group analysis did show a small improvement in women with menstrual irregularities taking CPA, possibly suggesting that antiandrogen treatment may work in women with hyperandrogenism. Opinions amongst clinicians treating female AGA do differ and there are those who strongly believe that antiandrogens are effective, but until we get proper RCTs, the controversy is likely to live on. Unfortunately, there is no commercial interest in the field, which makes funding such trials difficult.

Further differences emerge when we explore the genetics of female AGA. The few early studies, such as that of Osborn, assumed male and female AGA share the same genes and provided some evidence that this is the case. However, a twin study in women, although showing evidence for a significant genetic contribution to fronto-temporal recession and to hair graying, found none to hair thinning over the rest of the scalp, implying that hair thinning was non-genetic in origin and presumably had an environmental cause.¹⁵ This study was conducted

Ectodysplasin A2 Receptor: This is an isoform of ectodysplasin encoded by the ectodermal dysplasia gene. It is an integral component in epidermal and embryonic development and cell differentiation. Variants in EDA2R have been linked to the AR receptor role in androgenetic alopecia.

GWAS: Genome-wide association study is an examination of many common genetic variants in different individuals to see if any variant is associated with a trait.

WNT: WNT protein is a family of signaling molecules that regulate cell to cell interactions during embryogenesis. Abnormalities in these pathways have been linked to a number of clinical conditions.

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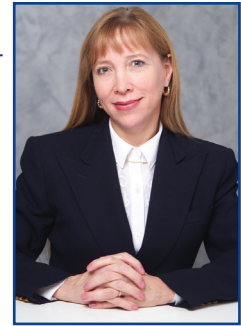
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President's Message

Sharon A. Keene, MD, FISHRS *Tucson, Arizona, USA* skeene@ishrs.org



As we begin a new year, I must acknowledge there were challenges we had to meet in 2014, but I am extremely proud of all of the accomplishments of the ISHRS over the past year. Since the inception of our Society, we have been committed to providing top quality education to our members and to encouraging physician excellence in the field of hair restoration surgery. For decades, we focused on science to enhance diagnostics and treatment of hair loss and researched ways to optimize surgical results—sharing our experience and knowledge to aid our colleagues in honing their skills. For a while, we were blind to an insidious and growing international blight on the public and the profession, in the form of the unlicensed practice of medicine in hair restoration surgery.

It has become known that some doctors have lent their names and medical license to a "hair restoration practice" but are not actually performing the surgery themselves. Instead, unlicensed assistants, who often learned the basic technical skills from experienced hair restoration surgeons, are now performing the surgery for some doctors with little knowledge or expertise in the field. This unethical practice is unbeknownst to many of the patients who intended and thought they paid for their surgery to be performed by an experienced medical doctor. However, every hair restoration surgeon knows safe surgery is more than knowing how to cut and place grafts. A technician who has not attended medical school and earned a medical license will not possess the skills to manage medical difficulties. In the past few years, we have learned of patients harmed by the unlicensed practice of HRS, and in the worst cases, even patient deaths.

With this information, it became incumbent on the Society to safeguard the public interest by publicizing this harmful and unethical practice to medical oversight bodies and the general public interested in HRS. So, in 2014, the ISHRS issued a consumer alert to caution doctors and the public against the unlicensed practice of medicine in HRS. Furthermore, we issued very clear guidelines on "critical to quality" aspects of surgery that the Society has deemed should be performed by licensed medical professionals. Additionally, the ISHRS bylaws have been changed so that moving forward, new surgical assistant members must be licensed medical professionals.

Furthermore, we have implemented a new membership application to encourage new physician members to join, but to also let them know the ISHRS has expectations of their ethical responsibility to patients, which includes the need to perform "critical to quality" aspects of surgery. New and renewing members are now required to attest their commitment to patient care and adherence to this standard.

All of these processes are the culmination of years of effort, but we as a Society know that to fulfill our commitment to excellence in patient care we have to act. We appreciate all our members who maintain and support these standards because doing so was the right thing to do, even before the Society placed these standards in writing. We also ask you to help us enforce these standards too, by letting us know if members are violating their attestation. Education is a priority for our attention and activities, but knowledge and skill without high ethical standards does little to garner public trust and provide optimal care.

Meanwhile, I am proud of all of our members who have supported these efforts. Any credit for improvements in results and patient care that accrue to patients will be shared with you, due to our collective efforts to promote these standards for all hair restoration surgery.

I wish you all the best for a happy and successful New Year! ♦

Co-editors' Messages

Mario Marzola, MBBS Adelaide, South Australia editors@ISHRS.org

Welcome everyone to the first edition for 2015. I wonder what this year will bring for all of us? Given that the economy in the “world out there” does not sound too good, we need to be thankful that we work in a field that is a little protected from the vagaries of the general economy.

It is a strong basic instinct for us all to feel good and look good, so as long as we treat the patients as people and not see them as business propositions, we are likely to grow our practice and end up better off than last year. That is my prediction. As noted in Dr. Russell Knudsen's Controversies article, hard selling, incentive selling, is not consistent with ethical medical practice. The tried and true medical practice principles are worth standing up for and common sense usually prevails as in this case.

Just when we start feeling comfortable in recognizing male pattern hair loss, it could be that 10% of our treated patients may actually have lichen planopilaris. Read Dr. Dow Stough's Editor Emeritus article. Have you ever had a patient who seemed to go bald again and lose his transplants? I have had one who lost most of his transplants over five years, maybe he had lichen planopilaris.

Dr. Bob True and I are so appreciative of all our regular columnists and none more than Dr. Sara Wasserbauer. How she manages to make interesting quizzes from so many different

subjects is beyond us, but a delight to read and to ponder all of the questions.

The subject of our lead article has fascinated me ever since I heard it presented in Korea last year. What does it mean? Female pattern hair loss is almost totally different genetically from male pattern hair loss! There are some ladies who lose hair because of higher than normal androgen levels or have higher sensitivity to androgens, but the majority may be losing their hair for totally different reasons. Multifactorial as Dr. Nusbaum suggests. Call it female pattern hair loss, not androgenetic alopecia. This is a big change, bringing forward more questions than answers, but that's life and that's what makes this field so interesting.

We hope you enjoy reading this first edition for 2015. Please send in questions, worries, concerns, or happy outcomes, we are interested in all of it. This year is again full of conferences and workshops. Take advantage of all the information available and attend at least one a year. That's how we become familiar with all the latest developments that help to give our patients the best outcomes. If we do that, then the business aspect of our practices will usually look after itself. ♦



Robert H. True, MD, MPH, FISHS New York, New York, USA editors@ISHRS.org

“It is our duty as men and women to proceed as though the limits of our abilities do not exist.” —Pierre Teilhard de Chardin.

I am always struck that the endless unknown exists not only in the vastness of the universe but also in the infinitesimal. It seems that the more we understand, the more of what we do not understand is disclosed. How incredible is it that a simple hair follicle can contain such an elaborate array of cellular and sub-cellular components. Although much is now understood about the cellular biology of the follicle, many processes remain to be defined and, to the point, we find that multiplication in the laboratory remains an elusive goal. As illustrated in the front-page article, we also find that long-held and cherished concepts of etiology must be rejected in order for us to move forward with more effective treatment. Perhaps with this issue we will declare that Female Androgenetic Alopecia as a term is now dead.

I am also struck by how often we fall into the trap of thinking of the world as being dichotomous—one right and one wrong. But this is simply a convenience, an escape. It always is more complicated. In Cyberchat, a simple question about preventing post-operative nausea and vomiting revealed how many different approaches we hair restoration surgeons are taking to anesthesia for our surgeries. Although very different, these various approaches work in their own way. I think as clinicians we often establish “our own way of doing things” and tend to adhere to these approaches to the point that they become almost mindless routine. It is key, however, that we keep an open mind, listen and learn from one another, and be willing to make alterations in our practices if we come across something that could potentially benefit our patients beyond what we are doing already.

I am a big fan of Dr. Barusco's Complications and Difficult Cases Column. Dr. Wasserbauer's MRSA case is valuable to us all. Her presentation of this case was one of the best parts of the Morbidity and Mortality Conference at the 2014 Annual Scientific Meeting in Kuala Lumpur. This was the second year of the M&M conference. I think all in all it was not as good as the first one. I felt the presenters spent too much time defending their care in their presentations. I am hopeful that the wonderful open and non-defensive give-and-take atmosphere of the first M&M in San Francisco will reappear in Chicago.

One of the most frequent misconceptions I encounter among patients who present for consultation is their belief that minoxidil is only effective for vertex balding. When I ask why they believe this they cite the package insert as saying it is only approved for balding in the vertex. Unfortunately, this myth prevents many from using this valuable treatment for frontal hair loss. The study cited by Dr. Donovan in Review of the Literature is clear confirmation that minoxidil does work for frontal loss. We all need to make sure our patients understand this, as it is such a commonplace public misperception. It would be valuable for the ISHRS to release a public announcement on this matter or even consider petitioning the FDA for a labeling change. I have also found that when a patient says they are using minoxidil, it is always a good idea to ask them to show me how they are applying it. If you are not doing this in your consultation, you will be surprised that a majority of patients are not using minoxidil correctly. Clarification and reeducation can be very valuable. ♦



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- Articles should be written with the intent of sharing scientific information with the purpose of progressing the art and science of hair restoration and benefiting patient outcomes.
- If results are presented, the medical regimen or surgical techniques that were used to obtain the results should be disclosed in detail.
- Articles submitted with the sole purpose of promotion or marketing will not be accepted.
- Authors should acknowledge all funding sources that supported their work as well as any relevant corporate affiliation.
- Trademarked names should not be used to refer to devices or techniques, when possible.
- Although we encourage submission of articles that may only contain the author's opinion for the purpose of stimulating thought, the editors may present such articles to colleagues who are experts in the particular area in question, for the purpose of obtaining rebuttal opinions to be published alongside the original article. Occasionally, a manuscript might be sent to an external reviewer, who will judge the manuscript in a blinded fashion to make recommendations about its acceptance, further revision, or rejection.
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Notes from the Editor Emeritus

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What If 10% of Your Cases Were Lichen Planopilaris “Incognito”?

Our bread and butter patients are men diagnosed with pattern alopecia. Dr. Rodney Dawber states that while the exact prevalence of pattern alopecia is not accurately recorded, it probably approaches 100% in the Caucasoid races. Terminal follicles are gradually replaced by vellus follicles, then attrition of vellus hairs occurs, a process occurring from puberty until death. Fortunately for us, the diagnosis is straightforward in most men. (For the purposes of this column, we will leave the discussion on female androgenetic alopecia for another day.) In textbook classical form, men present with typical Hamilton or Norwood patterns with non-scarring changes of their scalp. They may or may not be affected with varying degrees of seborrheic dermatitis.

Since the year 2000, we have heard a lot more concerns, presentations, scientific manuscripts, and hallway chatter that deal with the prevalence of lichen planopilaris (LPP) in hair transplantation. Was LLP present before or after the hair transplant? One such article reports 19 cases that developed following hair transplantation. It is almost as if cases of LPP, folliculitis, and cicatricial changes after transplantation seem to be on the rise. I suspect that increased awareness increases reporting in medical literature and better definitions of disease states are responsible and not an actual rise in occurrence. In my own practice, I have noticed a significant number of men with overt pattern baldness that come in for consultation displaying perifollicular erythema, subtle follicular hyperkeratosis, and questionable minute scarring along with physical findings that tend to fall outside the realm of androgenetic alopecia. These cases are often labeled by colleagues as early LPP or minimal or sub-clinical folliculitis. The typical patient who comes in is well informed on hair transplantation, appears to be a good candidate, is very knowledgeable of the procedure, is over age 30, and has pattern baldness with a Norwood II-V pattern. Upon exam, small punctate, white scars, and follicular erythema, with or without follicular keratosis, is often noted. Upon further inquiry, the patient has no idea what you are talking about when you question him further concerning scalp problems. He has never been treated for anything remotely related to a condition with the complicated sounding medical diagnosis of “lichen planopilaris.” Then that sinking apprehension sets in. Is this patient even a candidate for transplantation? Will I trigger LPP by operating on this patient? Am I worrying over nothing?

The above scenario is hardly a recent phenomenon among hair transplant surgeons. But what if up to 10% of all cases, typically diagnosed with common pattern alopecia, have these findings? Would we still be anxious to operate? What is the

prevalence and what risk are we taking by transplanting these cases? I have recently seen reports that up to 8% of all patients with a diagnosis of androgenetic alopecia on initial inspection will later manifest clinical findings of LPP. Our own esteemed colleague Dr. Gholamali Abbasi is diligently working in this area of research.

This brings us to an interesting classification dilemma. Are these really cases of early LPP (which will come to haunt us later) or simply that 5, 8, 10% of all androgenetic alopecia manifests subtle changes consistent with classical LPP. These may be normal “variants” that do not represent any disease state.

In the end, this may be more than simply “splitting hairs” over nomenclature. We all want our patients to do well and no one wants to fight folliculitis or

LLP for decades following a transplant. Biopsy in equivocal cases is often recommended, but is it really the answer? Biopsy involves both cost and delays. If the physician simply sees follicular erythema, follicular keratosis, and punctate scars, that is a pretty good indication there may be problems ahead. The pathology of early folliculitis, LPP, DLE, and folliculitis decalvans provides little insight into the ultimate clinical course of the patient. Until this mess is sorted out, we should raise up our antennas to be ever vigilant into those cases that display early subtle physical finding of LPP. We may have yet to fully appreciate all the subtleties of common baldness.

“Being able to handle a common problem with more insight and more efficiency, both in terms of coming to a diagnosis and in terms of developing a defined approach, I believe is of great importance to my colleagues.” —Vera H. Price, MD

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FAA from front page

in older women but it was performed in the same population and in a similar age group to one of the male twin studies that had shown a strong genetic contribution to male AGA. So far, we have no GWAS in women with AGA. However, using case control methodology, all 12 of the loci known to be associated with male AGA have been tested for an association with female AGA using DNA samples from German and UK cohorts. There was a weak association with the AR/EDA2 locus in the UK patients with early onset hair loss but not the German sample, and no association with any of the other 11 loci in either group (see table below).¹⁶⁻¹⁸

Gene Loci Associations in Pattern Hair Loss

Gene/Locus	Male AGA	FPHL
AR/EDA2R	+	+/-
20p11	+	-
1p36.22	+	-
2q35	+	-
2q37.3	+	-
3q25.1	+	-
5q33.3	+	-
7p21.1	+	-
7q11.22	+	-
12p12.1	+	-
17q21.31	+	-
18q21.1	+	-
ESR2	ND	+/-

These findings suggest there is some commonality between early onset male and female AGA, but otherwise imply there are significant differences in etiology. Two independent studies in women have suggested a weak association with the estrogen receptor gene ESR2,^{19,20} but, beyond this, we have little evidence for a genetic component to female AGA, in keeping with the results of the twin study. A GWAS will be needed to ascertain whether there are genetic associations in female AGA that are not present in men, but funding such a study has yet to be achieved.

Until we have better evidence for a role for androgens and genetics in female hair loss, the use of “female AGA” should perhaps be abandoned, hence the preference by others and ourselves working in the field for “Female Pattern Hair Loss” as a less committal descriptive term.

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Note from Dr. Bernard Nusbaum: At first glance, Dr. Messenger's article may appear to simply propose nomenclature, but more importantly, it should spark our thought processes regarding the multifactorial nature of female pattern hair loss. In the clinical setting, we recognize that patterns of hair loss in women are not as distinctive as in males. Moreover, our questioning of male hair loss patients generally centers on family history, whereby in women there might be no obvious familial predisposition and we want to know about nutritional status, deficiencies, systemic illnesses, hormonal changes (spontaneous or iatrogenic), toxic exposure, thyroid disease, or other endocrinopathies. I agree with Dr. Messenger that,

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