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COMMENTARY

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Frontal fibrosing alopecia: a disease fascinating for the researcher, disappointing for the clinician and distressing for the patient

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1 | A FASCINATING DISEASE FOR THE RESEARCHER

In just two decades since it was first described, FFA has gone from being a newly described disease entity to what is today considered by many dermatologists the most common clinical presentation of a primary scarring alopecia.[1] If only because of this epidemiological fact, FFA should be regarded by the scientific community as a very serious object of attention from a research standpoint.

In spite of FFA being so clinically distinctive and easy to diagnose since its inception, its aetiology has been elusive. In a recently published issue of *Exp Dermatol*, Tziotzios et al.[2] review the pathogenesis of FFA and draw attention to the particular need to investigate the genetic and/or epigenetic components associated with this disease. They highlight the growing recognition of FFA occurring in first-degree relatives and propose strategies to interrogate potential genetic contributions to this condition using deep sequencing of familial cases and genome-wide association study (GWAS) approaches. It will be interesting to see whether the GWAS of sporadic FFA cases currently underway identifies overlapping risk loci with other autoimmune conditions, as was recently identified by GWAS between AA and other autoimmune diseases.[3]

The relative contribution of these genetic processes to aetiology, however, needs to be viewed in the context of the epidemiology of this condition. The recent onset coupled with the steeply rising incidence of the disease in the last decade strongly points towards environmental factor(s) in disease aetiology. A recent cohort study by Aldoori et al.[4] suggests that leave-on facial cosmetics, particularly sunscreens, could be that long-suspected-but-never-found environmental factor. This study revealed that twice as many women in the FFA group regularly use a sunscreen compared to control, a difference that was highly significant. Moreover, patch tests performed with 40 FFA patients revealed a high frequency of positive reactions to fragrances. Unfortunately, leave-on cosmetics were widely used by women in general making discrimination of differences between these groups difficult. Follow-up work is currently underway exploring similar factors in male FFA patients as it is anticipated that differences in exposures will be more apparent between groups due to the much lower regular cosmetic usage in the male population as a whole.

If sunscreens are involved in the aetiology of FFA, it would be interesting to study the incidence of this disease in areas of different solar intensity. Intuitively, it seems reasonable to think that the prevalence of FFA should be higher in more central latitudes where women use sunscreens on an everyday basis. It might be coincidental, but as a matter of fact, FFA was first described in Australia, where the use of sunscreens as a preventive measure for skin cancer is widely used and has been recommended for many years.

2 | A DISAPPOINTING DISEASE FOR THE CLINICIAN AND DISTRESSING FOR THE PATIENT

The progressive course of this disease with the typical recession of the frontolateral hairline and loss of the eyebrows makes this condition very distressing to those affected[5]; something further aggravated by the lack of effectiveness of current medical therapies which, in the best-case scenario, can only stop its progression. Furthermore, many patients coming to hair transplant clinics as a last resort, hoping that hair transplantation may finally restore their receded frontal hairline, are disappointed when told that the permanent hair restoration achieved with hair transplantation in other hair disorders cannot be guaranteed in their case, since transplanted hair grafts may initially grow normally but usually become progressively affected and lost years later.[6]

Thus, unless a serendipitous discovery of an effective treatment suddenly appears, science will have to rely on insights into the pathogenesis of the disease in order to test medications that could be applicable to clinical practice. Since FFA and alopecia areata (AA) share a similar lymphocytic inflammation as part of an immune-mediated response associated with loss of immune privilege,[7] it would be advisable to test drugs that seem to work in AA or other autoimmune processes[8]: with the Janus kinase (JAK) inhibitors being prominent candidates. JAKs mediate signalling for various pro-inflammatory cytokines such as IFN gamma, IL-2, IL-4 and others. As FFA also displays a Th1-biased immune profile, IFN gamma-mediated IP collapse and increased interferon-inducible chemokine expression,[7] it is possible that JAK inhibition might also have a protective effect in FFA as well. Another candidate not currently used in FFA is Apremilast. This oral phosphodiesterase 4 inhibitor downregulates inflammatory responses, including a reduction of T-cell and NK cell cytokine production and reductions of interferon gamma. A recent study has shown that Apremilast suppresses experimentally induced alopecia areata in a humanized mouse model,[9] which makes this drug another potential candidate to test in FFA patients.

3 | CONCLUSION

It is likely that FFA represents a complex interplay between environmental factors and genetic predisposition. The work by Tziotzios et al. will undoubtedly further our understanding of FFA pathogenesis, potentially identifying disease processes currently unrecognized that could be targeted in future therapeutic strategies. Until then, concerted efforts are required to identify and modify environmental triggering factors, re-align currently available drugs for FFA therapy, improve the generally poor quality of FFA therapeutic evidence and perform well-designed clinical studies to test new and more effective therapies, ideally as topical formulations. So what can we do now? In addition to testing thyroid function, should patch testing now become a routine assessment in all FFA patients? How do we balance the possible risk of sunscreens in FFA against the clear health benefit of these products (i.e. anti-ageing and skin cancer protection) and communicate this in a safe and effective way to our patients? Clearly, many questions still need to be answered in this fascinating, frustrating and distressing condition.

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CONFLICT OF INTERESTS

The authors have declared no conflicting interests.

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