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The great atopic diseases epidemic: does chemical exposure play a role?

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ORIGINAL ARTICLE, p1255

Much research on the aetiology of atopic dermatitis has been focused on genetics, particularly regarding filaggrin. However, fundamental questions on environmental factors remain unanswered. Between 1964 and 1999 the prevalence of atopic dermatitis, hay fever and asthma in Aberdeen increased by 300%, 400% and 500%, respectively,¹ reflecting a general trend in industrialized countries. During the last decade this increased prevalence has persisted.² So what has caused this increase?

For many years the favoured explanation has been the 'hygiene hypothesis'.³ Over the last 50 years we have been having smaller families, and we encounter fewer microbes in childhood, so our immune systems do not mature so well. But the 'hygiene hypothesis', has been criticized for failing to explain several inconsistencies.⁴ One inconsistency, for example, is why infections with airborne viruses do not 'protect' from atopic allergic sensitization.⁴ So what else has changed in our lifestyle over the last 50 years? Exposure to protein allergens has been proposed by many as a key factor. The use of carpets and central heating has led to higher house dust mite exposure in some countries. But even with house dust mite as a causative influence on the development of atopic disease we again find conflicting and inconsistent results.^{5,6} Despite exhaustive global research into the role of microbes and protein allergen exposure in atopic disease pathogenesis, no consistent causality emerges. So, if these changes to our lifestyle are not the full answer, what are we left with?

The 'haptens-atopy' hypothesis postulates that increased haptens (includes contact allergens) and irritant chemical exposure during periods when there is already a natural tendency to T helper (Th) 2 immunological bias (maternal pregnancy and first year of life) contributes to the subsequent development of atopic disease in the child.⁷ Experimental cutaneous exposure to haptens can generally lead to two possible immunoreactive responses: classical allergic contact dermatitis, and also, alternatively, atopic dermatitis.⁸ Indeed many animal models of atopic dermatitis are based upon repeated cutaneous application of hapten chemicals.⁸ In such models, single elicitation exposure leads to a Th1/Th17-type cytokine response, but with repeated hapten application, a Th2-type cytokine

response becomes dominant, possibly orchestrated through innate immune mechanisms.⁷ Furthermore, certain occupations with a high hapten and irritant chemical exposure in maternal pregnancy are significantly associated with atopic disease in the subsequent child.⁹

Have we experienced an increase in hapten and irritant exposure over the last 50 years? The haptening of our personal environment over the last 50 years has been one of the major environmental changes in our lifestyle, however with little scientific comment. This has been effected by both cutaneous (household goods and toiletries with preservatives, surfactants and fragrances, dyes, metal jewellery) and oral [processed food, drugs (many of which are haptenic) and artificial milk] exposure. As just one example of lifestyle change, the frequent use of chemical-containing toiletries has been facilitated by indoor bathing facilities; in the first half of the 20th century an indoor bathroom with running water was a rarity; by 2000 indoor bathroom/showers were present in over 99% of households in the U.K.⁷ Between 1959 and 1976 there was a 250% global increase in the sale of toiletries (in real monetary terms) and most of this was in the industrialized countries, which also underwent a huge rise in atopic diseases.⁷

Thyssen and colleagues¹⁰ report a significant increased prevalence of allergic contact dermatitis in patients with atopic dermatitis. So atopic dermatitis is not just associated with protein allergy but, at least in adults, with chemical allergy too. While the exact significance of this is uncertain, the authors reflect that the relationship between atopic diseases and chemical exposure may be more 'intimate and complex' than previously supposed. Certainly, it is worthy of further research.

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Conflicts of interest

None declared.

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Winding the clock back on female androgenetic alopecia

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ORIGINAL ARTICLE, p 1314

Androgenetic alopecia (AGA) describes the replacement of terminal hairs on the frontal and vertex scalp with progressively finer, shorter and nonpigmented vellus hairs. The term AGA emphasizes the hormonal and genetic basis of the patterned hair loss that commonly affects both men and women and increases in frequency and severity with age.¹

The androgen-dependent nature of male pattern hair loss in men was demonstrated in 1942 when Hamilton² showed that baldness did not develop in 10 eunuchoid men, 10 men castrated before puberty and 34 men who had undergone orchiectomy during adolescence. Administration of testosterone led to the development of common baldness in those individuals who were genetically predisposed. When testosterone was discontinued the baldness did not progress but was not reversed.² No subsequent investigator has been able to challenge Hamilton's findings, and it is established beyond doubt that common baldness in men is androgen dependent.

The androgen-dependent nature of female pattern hair loss (FPHL) was inferred by many authors. Rook recognized that a mild degree of baldness (Hamilton types II–IV) may occur in women with normal systemic androgen metabolism, but stated that more extensive baldness is probably always associated with increased output of ovarian or adrenal androgens or both. He believed that normal female levels of androgens could induce baldness only in women with a strong genetic

predisposition: 'In the majority of women in whom the genetic predisposition is less strong, baldness is related to the degree to which the androgen output is raised. In a third group of women even grossly abnormal levels of androgens cause no clinically significant baldness, although all such patients are necessarily hirsute'.³

In 1977 Ludwig⁴ entitled his seminal paper 'Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex', reflecting the prevailing view of the time that ordinary baldness in both men and women was a variant of a single clinical syndrome.

This view that common baldness in both sexes was due to AGA was increasingly challenged in the late 1990s on the basis of the unpredictable response of FPHL to antiandrogen therapy, failure to demonstrate androgen excess in affected women, different peak ages of onset, rates of prevalence and patterning of hair loss, and case reports of women developing frontal hair miniaturization in the absence of androgens.^{5–7} In 2002 the Dermatological Consortium for Women's Health formally proposed the nomenclature for baldness in women be changed from female AGA to FPHL, pending further demonstration of androgen dependency.⁸

The discovery of gene loci for male AGA led to a number of attempts to resolve this issue through genetics.^{9–11} In this issue, Redler et al.¹² demonstrate shared genetic susceptibility loci between male and female pattern hair loss and conclude that the X-chromosome locus for the androgen receptor and ectodysplasin A2 receptor confers susceptibility to early-onset FPHL. While this shared genetic locus suggests a common androgen-related genetic factor, there also appear to be non-shared pathways such as the 20p11 locus, as well as the aromatase and the oestrogen receptor beta gene loci that may explain the phenotype differences between men and women with AGA.^{13,14}

In regard to the nomenclature describing this condition, it is now time to revisit the term AGA for describing the process in both men and women. FPHL can still be used to describe the phenotype, while the Sinclair and Ludwig scales describe the severity.

Conflicts of interest

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