Chemical-Induced Vitiligo

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KEYWORDS

• Vitiligo • Leukoderma • Chemical • Phenol • Rhododendrol • Monobenzone • Cellular stress • Autoimmunity

KEY POINTS

- Chemical exposure may serve as an environmental risk factor for developing vitiligo.
- Chemical-induced depigmentation is indistinguishable from vitiligo, and should be considered "chemical-induced vitiligo."
- Chemical-induced vitiligo is typically found at to the site of application and may also spread to remote, unexposed locations.
- Monobenzyl ether of hydroquinone was the first chemical noted to induce depigmentation in the skin, and is now used therapeutically in patients with vitiligo to complete their depigmentation.
- Most chemicals that induce vitiligo are phenols that act as tyrosine analogs to disrupt melanocyte function, resulting in autoimmunity.

INTRODUCTION

Like many autoimmune diseases, vitiligo pathogenesis is influenced by genetic, stochastic, and environmental factors. This is clear from the fact that first-degree relatives of patients with vitiligo have a 5-fold to 6-fold increased risk of disease and identical twins have a 23-fold increased risk, clearly implicating genetics as an important risk factor for vitiligo. However, despite sharing almost all of their genes, identical twins are only 23% concordant for disease, meaning that if one has vitiligo the other will have it only 23% of the time.[1] This clearly implicates other, nonheritable risk factors for developing vitiligo as well. Stochastic mechanisms, or the influence of random chance, likely play a role, particularly during the development of the immune system, which occurs through random recombination of T-cell receptors and antibodies. This process is responsible for "building" the autoreactive cells that ultimately attack melanocytes in vitiligo. The role of stochastic factors in developing vitiligo and other autoimmune diseases is not likely to account for all of the nongenetic risk, and so many believe that factors from the environment strongly influence the likelihood of developing autoimmunity.

Vitiligo is one of the few autoimmune diseases in which environmental factors are well-known, including the depigmenting effect of the chemical monobenzyl ether of hydroquinone (MBEH) discovered by Oliver and colleagues[2] in a tanning factory, but includes many others as well. Some have been directly implicated via topical challenge through patch testing, others through large population studies, and still others more indirectly. This article summarizes the chemicals that have been clearly implicated as causing or exacerbating vitiligo, as well as the mechanism by which this occurs. Recognizing these chemicals and their implications for managing vitiligo is important during patient counseling and follow-up, both when thinking about disease prevention, as well as improving therapeutic responses.

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CHEMICALS DIRECTLY IMPLICATED IN INDUCING VITILIGO

Monobenzyl Ether of Hydroquinone

In 1939, Oliver and colleagues[2] reported a case series of workers in a leather manufacturing company who developed patchy depigmentation on their hands and arms. In fact, 50% of the workers in this factory and others who wore a particular brand of gloves developed depigmentation on skin that contacted the gloves, and several of them also had similar lesions on remote areas that did not contact the gloves. The ingredients used in manufacturing the gloves were obtained by the medical team, and each systematically applied to the workers through patch testing. Only patches containing the antioxidant MBEH induced an inflammatory response, which was then followed by depigmentation. This chemical ingredient was removed from the gloves, and workers subsequently repigmented.[2] Depigmentation was also reported following exposure to other products that contained MBEH, primarily by items made of rubber.[3] MBEH has been removed from manufacturing in the US rubber industry, although may still be in use in other countries.[4]

After this observation, others attempted to use MBEH as a treatment for hypermelanoses[5–7]; however, reports of complete and irreversible depigmentation at the site of application and in remote areas limited its use,[8–11] and resulted in its removal from commercial products. The ability of MBEH to permanently remove skin pigment prompted Mosher and colleagues[12] to test it as a topical treatment for patients with severe vitiligo. They recommended the use of MBEH in patients with vitiligo who failed to respond to therapy with psoralen ultraviolet A (PUVA) and with depigmentation of more than 50% of their body surface area. Their retrospective study of 18 patients who used topical MBEH revealed that 8 patients completely depigmented in 4 to 12 months.[12] Since then, dermatologists have used this as a therapy in severe patients who desired it, noting also depigmentation remote from the site of application, and sparing of hair and eye color.[3] It is currently the only treatment approved by the Food and Drug Administration for vitiligo, and details about its use are in the article by Pearl Grimes, "Depigmentation Therapy for Vitiligo," elsewhere in this issue. In addition, monomethyl ether of hydroquinone has been reported to induce depigmentation in 2 subjects,[13] and has been used therapeutically to depigment patients with vitiligo.[14,15]

Hydroquinone, a chemical structurally related to MBEH and frequently used in skin-lightening agents, has not been clearly implicated in inducing or exacerbating vitiligo when used for cosmetic purposes. Despite many cases attributed to MBEH, only 2 patients reportedly developed depigmentation after exposure to photographic developing solution containing hydroquinone, and in both patients the depigmentation was preceded by allergic dermatitis.[16,17] However, despite the use of hydroquinone creams for many years, including to "feather" the border of vitiligo lesions to make them less apparent, it results in only uniform lightening of the skin, and no cases of focal depigmentation have been reported following this method of treatment.[3] Thus, hydroquinone-containing topical treatments are probably safe to use in patients with vitiligo who request treatment for coexisting hyperpigmentation (ie, melasma, for example), although this should be considered on a case-by-case basis.

4-Tert-Butylcatechol

The application of a single chemical-soaked patch to the skin was also used to implicate other phenols in products that induced depigmentation in patients with vitiligo. In the 1970s, a smaller percentage (4/75, ~5%) of factory workers in a tappet (valve lifters) assembly plant developed acral depigmentation due to contact with 4-tert-butylcatechol (4-TBC) present in a lubricating oil. All patients had severe inflammation before depigmentation at the site of contact, and three-fourths had remote depigmentation as well.[18] Patch testing with 4-TBC induced an inflammatory response in 3 of the 4 affected, with clear depigmentation in 1, whereas none of 6 healthy volunteers developed depigmentation.[18] Studies in guinea pigs confirmed the ability of 4-TBC to depigment the skin, particularly in high concentrations and in strong solvents.[19]

4-Tert-Butylcatechol and 4-Tert-Amylphenol

Bajaj and colleagues[20] reported the characteristics of 100 consecutive patients who presented with depigmentation under their bindi, a decorative item worn on the forehead of many Indian women, often using an adhesive resin. Seventy-three exhibited dermatitis at the site before depigmentation, and 34 had depigmentation remote from the site of bindi application. On patch testing of 15 patients with the adhesive resin, 5 had irritant reactions and 3 of those depigmented 15 to 60 days later. The chemical 4-tert-butylphenol (4-TBP) was the suspected culprit based on its high content in the samples tested, as well as a number of other reports that implicated the chemical in other occupations. An additional report