Role of chemical exposure in the incidence of vitiligo: a case–control study in Tunisia

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Abstract

Vitiligo is a multifactorial dermatosis with many etiological hypotheses that have been suggested for its occurrence. To our knowledge, few epidemiological studies are available on vitiligo induction factors and particularly on the role of exposure to chemicals in the onset of the disease has been found. Therefore, there is need to investigate the relationship between vitiligo and chemical exposures in order to understand this mysterious disease. We conducted a case–control study of patients with vitiligo whose diagnosis was made by a specialist in dermatology. The total study period was of 6 months extending from 1 July to 31 December 2019. The minimum sample size was determined as 46 cases and 92 controls. The control group was gender, age, and professional status matched to the vitiligo group. In the binary logistic regression model, household chemicals/colored toothpaste use, a history of a repeated antibiotic use, and an occupational exposure to phenol/catechol derivatives were significantly associated with vitiligo (three to fourfold increase). Our results suggest that chemical factors play a key role in the occurrence of vitiligo. Therefore, prevention of this dermatosis requires the identification of exposure to the incriminated chemicals in any patient followed for vitiligo. The earlier the diagnosis of ‘chemical’ or chemically aggravated vitiligo, the better the prognosis for this disease.

1. Introduction

Vitiligo affects around 0.1–2% of the world’s population [1]. It results from a continuing and selective destruction of some or all of the melanocytes residing in the interfollicular epidermis and occasionally in the hair follicles [2]. From a pathophysiological point of view, vitiligo is a multifactorial dermatosis with many etiological hypotheses that have been suggested for its occurrence. To date, the association of environmental, autoimmune, and genetic factors has been retained to explain this autoimmune destruction of melanocytes [3]. Among the environmental factors, numerous precipitating factors have been implicated in the induction of vitiligo, such as sunburn, hormonal factors, stress, mechanical factors, and cytotoxic chemical factors. Several experimental evidences have shown that melanocytotoxic chemicals, especially phenolic and catechol derivatives, could cause vitiligo [4–7]. To our knowledge, few epidemiological studies are available on vitiligo induction factors and particularly on the role of exposure to chemicals in the onset of the disease has been found [8]. Therefore, there is a need to investigate the relationship between vitiligo and chemical exposures in order to understand this mysterious disease.

2. Subjects and methods

2.1. Setting and participants

We conducted a case–control study of patients with vitiligo whose diagnosis was made by a specialist in dermatology with clinical examination and Wood’s light, and who were followed up at the dermatology department of the Hedi Chaker University Hospital of Sfax. The total study period was of 6 months extending from 1 July to 31 December 2019. Patients diagnosed with acquired hypopigmentation disorders other than vitiligo such as physical trauma vitiligo or post-inflammatory depigmentation were not included in this study.

Sample size was calculated using an online calculator available on the BiostaTGV website (Epicalc 2.9.0.1 package) (https://biostatgv.sentiweb.fr). The minimum detectable odds ratio was fixed to 3 according to a multicenter collaborative study by the Korean Vitiligo Society on the occupational risk factors causing vitiligo where frequent chemical occupational exposure of the hands was considered as a risk factor of vitiligo with an OR = 3.02 [9]. The expected proportion exposed in controls was fixed to 0.33. It was set with reference to the results of the 2010 SUMER survey on the medical surveillance of exposure to...
occupational risks and showing that in France in 2010, 33% of employees were exposed to at least one dangerous chemical agent [10]. We enrolled two controls per case, with no history of dermatological or autoimmune disease, per case for a better statistical power which was set at 0.8 with an alpha error risk of 0.05. The minimum sample size was determined as 46 cases and 92 controls. These controls were randomly recruited from the general population, who did not have any history of vitiligo or other acquired hypopigmentation disorders and who voluntarily agreed to participate in our study. They were gender, age, and professional status matched to the vitiligo group.

2.2. Methods and measurements

Data were collected through direct interviews conducted by the same doctor with the participants. It was completed by the exploration of medical records and consultation sheets. Collected data consisted of the following parts:

1. Sociodemographic characteristics: gender, age, professional status, and rural or urban origin.
2. Data regarding environmental chemical exposure: having a residence near a polluting site (a polluting site was defined as any source located less than 200 m near the residence if it was a service station or small factory and less than 1 km if it was a large factory polluting the environment), histories of household chemicals, the use of a colored toothpaste, hair dye, cosmetics, deodorants, or perfumed oil.
3. Medical characteristics: a family history of vitiligo, a history of a repeated antibiotic use, and characteristics of vitiligo (duration, clinical aspect, type, and disease' course). We used the Vitiligo Extent Score (VES) to calculate the affected body surface area (BSA) [11].
4. Data regarding occupational chemical exposure preceding the onset of vitiligo: activity sectors and jobs occupied for more than 6 months, professional tenure, and exposure to the following chemicals according to the activity sector [12]: Mono-Benzyl Ether of Hydroquinone (MBEH), additional phenol catechol derivatives, detergents/disinfectants, and insecticides/pesticides.

2.3. Statistical analysis

We used R-statistical software, version 4.0.1 to perform all statistical analyses [13]. In the descriptive analysis, for both cases and controls, we determined frequencies and percentages for qualitative variables, means, standard deviations, and the range of extreme values for quantitative variables. We used the chi-square test to compare between categorical data and Student’s t-test for comparisons between continuous variables in the bivariate analysis.

Risk factors associated with the induction of vitiligo were issued from a binary logistic regression with a backward procedure. Adjustment for age, gender, professional status, and genetic factors (family history of vitiligo) was carried out preliminarily in the case–control analysis. For all analyses, a level of significance of p < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the study population

Female predominance was noted in both case and control groups (M/F sex ratio = 0.84). More than half of the population was in the labour force. Among vitiligo patients, the mean duration of the disease was 9.8 ± 10.7 years. The most common type of vitiligo was non-segmental vitiligo (69.6%). Patients were suffering from active disease in 43.5%. The mean BSA score was 4.2 ± 5.1% (Table 1).

3.2. Association between chemical exposure and vitiligo occurrence

In the bivariate analysis, several significant associations were found between the case and control groups. Living near a polluting site was considered a risk factor for developing the vitiligo (p = 0.00; OR = 3; 95% CI = [1.33–6.79]). Other environmental chemical factors increased the risk of vitiligo occurrence such as household chemicals use (p = 0.00; OR = 2.6; 95% CI = [1.27–5.55]) and colored toothpaste use (p = 0.02; OR = 2.89; 95% CI = [1.10–7.61]). We also found that having a history of a repeated antibiotic use increased the risk of vitiligo occurrence by 5.1 folds (p = 0.00; IC95% = [2.26–11.49]). A significant association was found between occupational chemical exposures to phenol catechol derivatives and vitiligo (p = 0.01; OR = 2.9; 95% CI = [1.18–7.12]).

In the binary logistic regression model, household chemicals/colored toothpaste use, a history of a repeated antibiotic use, and an occupational exposure to phenol catechol derivatives were significantly associated with vitiligo (three- to fourfold increase) (Table 2).

4. Discussion

In this case–control study, we explored the association between vitiligo and the environmental and occupational exposure to chemicals. Our results
Table 1. Characteristics of the case and control groups.

| Characteristics                                      | Vitiligo (n = 46) | Control (n = 92) | p-value |
|-------------------------------------------------------|-------------------|------------------|---------|
| **a. Sociodemographic characteristics**               |                   |                  |         |
| Age (mean ± SD years)                                 | 44.1 ± 13.7       | 43.8 ± 13.3      | 0.92    |
| Gender                                                | 25 (54.3)         | 50 (54.3)        | 1       |
| Male                                                  | 21 (45.7)         | 42 (45.7)        |         |
| Professional status                                   | 26 (56.6)         | 52 (56.6)        | 1       |
| Employed                                              | 1 (2.2)           | 2 (2.2)          |         |
| Unemployed                                            | 13 (28.3)         | 26 (28.3)        |         |
| Housewife                                             | 2 (4.3)           | 4 (4.3)          |         |
| Student                                               | 4 (8.7)           | 8 (8.7)          |         |
| Retired                                               |                   |                  |         |
| Origin                                                | 24 (52.2)         | 37 (40.2)        | 0.18    |
| Rural                                                 | 22 (47.8)         | 55 (59.8)        |         |
| **b. Medical characteristics**                        |                   |                  |         |
| Family history of vitiligo                            | 15 (32.6)         | 26 (28.3)        | 0.59    |
| History of a repeated antibiotic use                  | 22 (47.8)         | 14 (15.2)        | **0.00**|
| Disease duration (mean ± SD years)                    | 9.8 ± 10.7        | -                |         |
| Clinical aspect                                       | 32 (69.6)         | -                |         |
| Non-segmental                                         | 14 (30.4)         | -                |         |
| Segmental                                             | 0                 | -                |         |
| Universals                                            |                   |                  |         |
| Initial progression of vitiligo                       | 29 (63)           | -                |         |
| Slow                                                  | 14 (30.4)         | -                |         |
| Rapid                                                 | 3 (6.5)           | -                |         |
| Very rapid                                            |                   |                  |         |
| Lesions’ morphology                                   | 4 (8.7)           | -                |         |
| With hyperpigmented border                            | 29 (63)           | -                |         |
| Totally depigmented                                   | 13 (28.3)         | -                |         |
| Confetti lesions                                      |                   |                  |         |
| BSA (mean ± SD%)                                      | 4.2 ± 5.1         | -                |         |
| **c. Environmental chemical exposure**                |                   |                  |         |
| Residence near a polluting site                       | 17 (37)           | 15 (16.3)        | **0.00**|
| Household chemicals use                               | 30 (65.2)         | 38 (41.3)        | **0.00**|
| Colored toothpaste use                                | 11 (23.9)         | 9 (9.8)          | **0.02**|
| Hair dye use                                          | 19 (41.3)         | 28 (30.4)        | 0.20    |
| Cosmetics use                                         | 9 (36)            | 10 (20)          | 0.13    |
| Deodorants use                                        | 30 (65.2)         | 72 (78.3)        | 0.11    |
| Perfumed oil use                                      | 9 (19.6)          | 11 (12)          | 0.23    |
| **d. Occupational chemical exposure to**              |                   |                  |         |
| MBEH                                                  | 5 (10.9)          | 5 (5.4)          | 0.24    |
| Additional phenol/catechol derivatives                | 13 (28.3)         | 11 (12)          | **0.01**|
| Detergents/disinfectants derivatives                  | 4 (8.7)           | 1 (1.1)          | 0.07    |
| Insecticides/pesticides                               | 10 (21.7)         | 10 (10.9)        | 0.08    |

showed similar significant associations in bivariate analysis and in the binary logistic regression model. Males and females are equally affected by vitiligo, although women and girls tend to consult more often [14] like our study. The mean age of our patients was 44.1 years. Vitiligo develops at all ages, but usually occurs in young people between the ages of 10 and 30 years [15]. A recent epidemiological study of vitiligo age-of-onset in Caucasians showed dramatic delays in vitiligo age-of-onset (by more than twofold), especially from 1973 to 2004, suggesting that exposure or biological response to a key vitiligo environmental trigger diminished during this period [16]. In the literature, from this exposure to chemical factors was born the terminology of ‘chemical’ vitiligo versus idiopathic vitiligo [17]. The role of environmental pollution in causing this disease is not inconsiderable. About 80% of vitiligo risk is attributable to genetic factors, and the rest (20%) is attributable to the environment [1]. In our study, living near a polluting site increased the risk of vitiligo by 3 times. This is consistent with other studies where it was found that vitiligo has a higher incidence among those who live near some polluting industries [18]. We also found that the use of household chemicals and colored toothpaste

Table 2. Multivariate analysis of chemical risk factors for vitiligo occurrence.

| Variable retained in the model                  | Exp (B) | OR   | 95% CI | p-value |
|------------------------------------------------|---------|------|--------|---------|
| Household chemicals use                         | 1.21    | 3.36 | [1.42–8.44] | **0.00**|
| Colored toothpaste use                          | 1.18    | 3.27 | [1.03–10.67] | **0.04**|
| History of a repeated antibiotic use            | 1.54    | 4.67 | [1.86–12.25] | **0.00**|
| Occupational exposure to phenol/catechol derivatives | 1.53    | 4.63 | [1.55–14.59] | **0.00**|
| Occupational exposure to insecticides/pesticides | 1.11    | 3.03 | [0.92–10.09] | 0.06    |
| Residence near a polluting site                 | 0.94    | 2.56 | [0.97–6.86] | 0.05    |
was a risk factor for developing vitiligo. In fact, ‘chemical’ vitiligo, a disease of industrial origin, was subsequently also found to be induced by certain chemicals for household use [19]. Contributing chemicals have been reported in various products such as lipstick, hair dye products [20], deodorants, detergents, cleansers, fragrance oils, insecticides, pesticides, rubber sandals, socks/shoes black [21], and colored toothpastes [22]. All of these findings can be explained, on the one hand, by the widespread use of phenols as ingredients in commercial household products [12]. On the other hand, these products can cause oxidative stress which plays a key role in vitiligo’ pathogenesis according to several scientific evidences [23].

Interestingly, occupational exposure to phenols and catechols increased by 4 times the risk of vitiligo. The working mechanism of MBEH is explored in comparison to 4-tertiary butyl phenol (4-TBP), a known causative agent for occupational vitiligo mediating apoptotic melanocytic death. Cytotoxic experiments reveal that similar to 4-TBP, MBEH induces specific melanocyte death [6]. Moreover, MBEH exposure upregulated the levels of melanogenic enzymes in cultured melanocytes and skin explants, whereas 4-TBP reduced the expression of the same. In summary, exposure to MBEH or 4-TBP has profoundly different consequences for melanocyte physiology and activates different death pathways.

In addition to these risk factors, we found that having a history of a repeated antibiotic use caused presumably vitiligo in our patients. The action of antibiotics on skin pigmentation has been studied on the animal model (mouse) and has been explained by their actions on both the microbiome and the immune system [24]. Das et al. highlight cases of chemical leucoderma related to hydroquinone used in skin-lightening creams [25]. Our study has several limitations worth noting. Interviewees may be subject to a memory bias that is inherent in all case–control studies owing to its retrospective nature. In addition, the past chemical exposure assessment was based on a qualitative analysis. It was not possible to approach a quantification of exposure to these products far back in the past. As a result, this assessment may be considered as subject.

Despite these limitations, we consider our study to be pilot and open one. In the future, we would like to conduct a prospective study to evaluate the impact of the evasion of exposure to products implicated in the induction or aggravation of vitiligo with the aim of improving the prognosis of this dermatosis.

5. Conclusion

Vitiligo is a mysterious, multifactorial, and complex disease. The role of environmental, autoimmune, and genetic factors is still not well defined. Our results suggest that chemical factors play a key role in the occurrence of vitiligo. Therefore, prevention of this dermatosis requires the identification of exposure to the incriminated chemicals in any patient followed for vitiligo. The earlier the diagnosis of ‘chemical’ or chemically aggravated vitiligo, the better the prognosis for this disease.

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