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The Epidemiology of Vitiligo

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Abstract Vitiligo is a common condition seen in a dermatology office, which has a variety of comorbidities. Worldwide, the prevalence of vitiligo ranges from 0.4 to 2.0 %, with regions of greater or lesser prevalence. Most studies demonstrate slightly greater prevalence in females and 50 % onset in childhood, but exceptions to these rules exist. Childhood vitiligo has been associated with atopic diathesis, halo nevi, and family history of vitiligo and autoimmunity. Post-pubescent vitiligo has been associated with greater acrofacial disease and thyroid disease, and early data supports reduced non-melanoma and melanoma skin cancer risk. Disease severity is inversely proportional to distance from the equator, and birthplace outside the USA may be somewhat protective against severe disease. This article reviews the epidemiology of vitiligo and the epidemiologic relationship of vitiligo to comorbid diseases and family history, with a focus on recent literature.

Keywords Dermatology · Pediatrics · Post-pubescent · Comorbid diseases · Family history · Literature review

Introduction

Vitiligo is a common autoimmune depigmenting disorder with a variety of comorbidities [1]. The following article is a review of epidemiologic aspects of vitiligo, with a focus on recently confirmed data on the topic. Little alteration in incidence or presentation has occurred from historic data; however, some important conceptual themes are emerging in the literature including differences in epidemiologic associations for children 12 and under and post-pubescent patients as well as location-specific environmental factors that impact age of onset of disease.

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Prevalence and Demographics of Vitiligo

Estimates of the prevalence of vitiligo are rarely based on population-based studies. The limited data that exists is reviewed herewith. There are two notable subsets of vitiligo patients: group 1, those with onset at or before age 12 years, and group 2, those who are older than 12 years of age. Group 1 has more family history of vitiligo and canity, halo nevi, Koebner phenomenon, segmental disease, and atopy. Group 2 has more acrofacial disease and comorbid thyroid disease [2]. In populations where incidence occurs early in life, e.g., parts of India, the age of onset and comorbidities will be closer to group 1, where the mean age of onset was 6.9 years and family history was noted in about one quarter of patients [3]. Two populations, Denmark and Greece, have been described where the populous is similar to group 2 with respect to the distribution of age of onset. In an 8-year study of 50,237 dermatologic patients seen from 1995 to 2002 in Greece, the relative prevalence was 0.5 % and median age 38 years in women and 43 years in males. The majority of cases detected in children 0–10 years were noted in females (0.8 vs. 0.3 prevalence in females vs. males). For the 30 year and under category, the prevalence for females is twice that of males, 0.6 vs. 0.3. For patients over 60 years, the prevalence was 0.5 % for both males and females [4].

A similar pattern with ongoing incidence with advancing age has been noted in a prevalence study of 47,033 individuals in Bornholm, the fifth largest of the islands of Denmark, in historic data from 1971 to 1972 where only 0.09 % of children

less than 10 years of age and 0.15 % for ages 10–20 years manifest disease vs. 0.9 % of adults aged 60–69 years, with decline in incidence at age 70 years and afterwards (total was 179 patients with vitiligo). In this study, the mean age of onset of disease in vitiligo patients was 38.7±19.5 years for men and 36.7±18.9 years for women [5]. Based upon this, there are clearly environmental factors, e.g., vitamin D levels and sun exposure, that mitigate disease onset, some of which are reviewed later in the paper.

Most populations have mixed age-of-onset groups and double peaks as has been noted by Ezzedine et al. [2]. Onset of vitiligo is usually before age 30 and most studies demonstrate half of patients have onset by age 20 years [6, 7]. In cohorts from Riyadh and from Brazil, the mean age of onset was 17.22 and 25.25 years of age [8, 9]. When early onset is noted in children it may correlate with presence of family history of disease. In a study of pediatric vitiligo from Uttarakhand, India, 35.2 % of patients were pediatric (less than or equal to 12 years of age) [10]. The mean surface area involved in another study was 14 % [11].

Overall Prevalence of Vitiligo

The prevalence of vitiligo in a dermatology clinic population in Lagos, Nigeria, examined in October 2003–October 2006 was 2.8 % [12]. In men over the age of 40 years seeking prostate screening, 0.7 % had genital vitiligo in Brazil [13]. There are some sunny climates that appear to have a mild reduction in vitiligo prevalence; for example, in the West Indies, prevalence is 0.34 % [14]. Kruger and Schallreuter have reviewed the worldwide prevalence of vitiligo in 2012, with an extensive and in-depth review of prevalence data from more than 50 worldwide studies. They summarized that the prevalence of vitiligo ranges from a low of 0.06 % to a high of 2.28 % [15]. The prevalence data derived was specific for China, Romania, Denmark, India, Germany, and Uzbekistan based on population-based samples, yielding the best data in these populations. They conclude that worldwide prevalence generally lies within a range of 0.4–2 % [15].

Jacobsen et al. created an estimated population burden for 24 autoimmune diseases in the USA, published in 1997, based on mean weighted prevalence and incidence rates from reported studies available at that time including four vitiligo studies—one from Denmark discussed above [5]; one from Gujarat; one from Calcutta, a review of the CDC Summary of Notifiable Diseases in the USA published in the 1994 MMWR; and one from a study of thyroid disease in diabetic patients. The authors acknowledged that there were no population-based studies for North America from 1965 to 1995. Based on the limited data they had, the authors generated a weighted mean prevalence of 400.2 per 100,000 with 52.3 % being female. They further estimated for 1996 that there were 1,059,560 persons with disease in the USA [16].

In a cohort of 140 consecutive dermatology patients presenting to a private dermatology practice in Winston-Salem, NC, USA, all patients were evaluated for a pigmentary disorder. Eighty percent of patients had one or more pigmentary disorders; 47.3 % of patients were self-conscious about their skin appearance and 32.7 % felt unattractive due to their skin pigmentation. In this cohort, vitiligo was noted in only one patient. If this was a representative sample from the USA, the prevalence would be 0.7 % [17].

Alkhateeb et al. surveyed 2624 probands in North America and the UK regarding their vitiligo. They project a population-based prevalence of 0.4 % for vitiligo in the combined regions, with a projected female prevalence of 0.41 % and male prevalence of 0.39 %. In this series, 83 % of probands derived from online vitiligo support groups were Caucasian, with approximately equal female and male respondents. The rate of siblings being affected was 6.1 % and concordance in monozygotic twins was only 23 %. In the USA/Canadian component of the cohort (n=856), 28 % were male, 72 % female, 78 % Caucasian, 8 % Hispanic, 4 % African-American, and 1 % Asian. Therefore, this sample is likely to be more representative of the demographics of participants in online vitiligo support groups [18].

A recent study from Rome looked at 10,040 vitiligo patients. In this group, 5457 were female (54.4 %) and 4583 were male (45.6 %). Six thousand four hundred eighteen were under the age of 40 years (63.9 %), 2703 were between 40 and 60 (27.8 %), and 919 were over 60 years of age (9.2 %), demonstrating the relatively uncommon appearance of the disease in patients over the age of 60 years [19]. A recent review of 1010 patients from a Gujarat (Indian) dermatology clinic identified a female predominance of 57.3 %, and most cases had onset by age 30 years—6 % in the first decade, 22.3 % in the second decade, and 24.8 % in the third decade. Only 4.3 % had onset after age 60 years. Of these patients, 91.3 % were vegetarians and 60.9 % had a progressive course. The lower limb was the leading site of onset with 41.5 % presenting with lesions in this location, 11.7 % for the upper extremity, and involvement of the leg was noted in 75.7 % followed by the upper limb 68.3 %, face 50 %, trunk 45.7 %, leukotrichia 10 %, and genital disease 6.7 % [6].

Although vitiligo is common worldwide at 0.5–2 % prevalence, there are pockets of India (Gujarat) that are estimated to have an incidence of 8.8 %, suggesting strong genetic and perhaps environmental contributions [15].

Pediatric Prevalence of Vitiligo

The prevalence of vitiligo in a cohort of children attending a dermatology clinic in Nepal (n=1086) was 2 % [20]. In China,

a recent population-based study showed a vitiligo disease incidence of 0.56 %. In a Nigerian series from 2003 to 2006, 35.5 % of patients were age 20 or less [12]. A study of Taiwanese school children showed a prevalence of 0.09 % [21]. As in adulthood, pediatric disease may be minimized in extremely sunny climates; for example, in the Sinai desert, the incidence of childhood vitiligo is extremely low at 0.18 % [22]. Kruger and Schallreuter have reviewed the worldwide prevalence of pediatric vitiligo and cite the prevalence as 0–2.16 % [15].

Demographics in the USA

Data in the USA is not based on good population-based techniques. Lerner et al. attempted to identify patients via word of mouth and came up with an incidence of 0.19 % in Nevada, MO, and 0.15 % in Pendleton, OR; however, these populations may not have been ethnically diverse, therefore not being truly generalizable to the entire US population [23]. Alkhateeb projected combined North American and UK prevalence to be 0.4 % [18].

A review of 477 vitiligo patients derived from a comprehensive database from the Henry Ford Health System in Detroit, MI, from 2001 through 2006 created sample demographics of patients seeking care in the USA. In that sample, 42 % were Caucasian, 29 % African-American, 6 % Asian/Pacific Islander, 2 % Hispanic, 2 % Middle Eastern, 2 % Native American, and 17 % unavailable for comment. Males constituted 48.9 % of cases, and 33 % of patients were under the age of 18 years, 39 % 18–49 years, and 28 % over 49 years of age. The authors did not project an estimated prevalence for vitiligo for their population but projected skin cancer prevalence in vitiligo, which will be reviewed later in the manuscript [24].

In a pediatric study of 140 children with vitiligo in the Chicago, IL, area, 52.6 % were Caucasian, 22.6 % Hispanic, 12.4 % Asian, 8 % African-American, and 2.9 % Middle Eastern [25]. Prevalence was not specified in either cohort.

Sheth et al. surveyed a large database of adult patients and identified 3280 patients identified from a Research Patient Data Repository from a Boston, MA, teaching hospital. Patients were identified from January 2000 to June 2011. In this vitiligo cohort, being female was predominant (57.6 %) and 56.9 % were Caucasian [26].

Site of Disease

Head and neck was the leading site in another study. In a pediatric cohort from Chicago, head and neck involvement was most common at 36.5 % [25]. In an Indian cohort of mixed-age group, legs were the most common site noted in about half of patients [27]. Legs were also the most common site of onset in a series of patients from Dhaka, Bangladesh [28]. Similar to the Pajvani et al. study [25], a cohort of Korean children had head and neck disease in 58.8 %, confirming this is the leading site of disease for children [29].

Family History

Family history appears to lie between 15 and 20 % in most studies. In a Chinese survey of 815 probands, family history was 15.7 % [30]. In a Gujarat survey, 20.4 % had a family history of vitiligo [7]. The lowest family history rate I can identify is 3.43 % in a cohort of 30,000 patients from Mumbai [31]. Even within a single country, pockets of differences do exist. A survey of 137 children with vitiligo in the USA comparing to control patients found positive predictive values of family history of vitiligo, leukotrichia, and/or autoimmunity with onset of disease before age 7 years [25]. The rate of familial vitiligo in first- or extended-degree relatives was 30.7 % (first degree 8.8 %; second degree 21.9 %) [25]. A similar associated family history of 34 % was noted in a study from the Island of Martinique [14].

Consanguinity can account for elevated incidence in certain regions of the world. In the Qassim Region of Saudi Arabia, a study of 111 vitiligo patients (61 male; 50 female) demonstrated consanguinity in 32.4 % of cases and first-degree cousin consanguinity in 22.5 % of cases. Consanguineous cases had an earlier age of onset [32].

Prevalence of Vitiligo Types

Disease types vary by location. Generalized vitiligo (Non-segmental vitiligo) is most common. In India (Gujarat), 85 % of patients have generalized disease (vulgaris 57.4 % and acrofacial 27.6 %) [6, 7]. Segmental disease was seen in 6.6 %, universal 6.9 %, and mucosal limited 1.5 %. Generalized disease is most common and is seen in one third to two thirds of patients [33–35].

Segmental disease affects a third in a recent Indian cohort to less than 8 % of children in a study from Jordan [36]. In the Jordanian study, 2000 consecutive children evaluated yielded 71 children (3.6 %) with vitiligo, 0.45 % aged <1 year, 1 % aged 1–5 years, and 2.1 % aged 5–12 years. Non-segmental-type vitiligo was seen in 67 of the Jordanian children (92.9 %) [37]. Segmental disease is more common with early onset and can account for almost a third of pediatric cases [38, 39]. Patients with segmental disease have fewer lesions, less body surface area involvement, and no elevation of thyroid disease risk [40–42]. The presence of halo nevi and leukotrichia in segmental disease highlights the presence of a greater risk of later generalized disease, i.e., the mixed-type vitiligo [43].

Comorbid Disease (Table 1)

Comorbid autoimmunity and inflammatory conditions are common in vitiligo. A Gujarat cohort had comorbid alopecia areata in 1.9 %, lichen planus 0.7 %, thyroid disease 0.7 %, psoriasis 0.4 %, and atopic dermatitis 1 % [6]. Thyroid disease in Tabriz, Iran, is three times more common in vitiligo than in the control group (p=0.008) [7]. Among the patients, 4.7 % have elevated fasting blood glucose [7]. About 20.3 % of Japanese [44] and 40 % of Turkish vitiligo patients will have a secondary autoimmune disease [45]. On the lower end of the spectrum, a cohort from Mumbai of over 30,000 dermatology patients was evaluated and the incidence of comorbid autoimmunity with vitiligo was projected to be 2.94 %; however, this grouping also had limited family history at only 3.43 % [46].

In the same cohort from Turkey with a mean age of 37 years, it was demonstrated that 55 % of 80 patients with vitiligo had comorbid autoimmunity [47]. Thyroid autoimmune disease is common in children with vitiligo of the generalized type, ranging from 11 to 26 % in older studies from Italy and New York [44, 48] and more recently 25.3 % (14.6 % Hashimoto's) in Serbian children and adolescents [49].

Sheth et al. reviewed 3280 patients with vitiligo through a computerized database of US patients. In this cohort, 23 % had autoimmune comorbidities. In a cohort of children from The Netherlands, active thyroid disease was noted in 6.2 % and about 10 % of patients had silently elevated antibodies (anti-TPO) [26]. A meta-analysis of studies looking at thyroid disease in vitiligo from 1968 to 2012 showed thyroid disease, autoimmune thyroid disease, and presence of thyroid-specific autoantibodies and a mean prevalence of, respectively, 15.1, 14.3, and 20.8 % in patients with vitiligo and a relative risk (RR) of, respectively, 1.9, 2.5, and 5.2 (all statistically significant). The risk increased with age in this cohort [50]. Another controlled sample of 50 children with vitiligo demonstrated that thyroid disease was correlated to duration of illness but not age of onset [51].

Hearing issues were noted in 37.7 % of Turkish patients surveyed. Sensorineural hearing loss can occur and screening is helpful when the question exists [52]. Specific abnormalities noted are common, including increased latency of wave III and prolongation of the interlatency peak between wave I and II. No correlation was noted between age, disease parameters, and hearing loss [53].

The Koebner phenomenon can be seen in a small group as seen in Turkey (7.5–11.48 %) [49, 54] or a larger group (20.8–31.3 %) [6, 3, 36] and may be more common in the younger patients. Halo nevi can be seen in 3.8–5.9 % of patients [55, 34] and are forme fruste of non-segmental vitiligo [2, 44]. As mentioned previously, Ezzedine et al. have noted these nevi to be more common with early-onset disease and to portend risk of generalized vitiligo in children with segmental disease [44]. Antinuclear antibodies can be elevated and incidence varies from 3.5 % [7] to 41 % in the Sheth cohort, suggesting Caucasian patients are at greater risk [26].

Patients with diabetes are more likely to have vitiligo, having an incidence of 4.9 vs. 1.8 % of controls [55]. In a cohort of adult patients with autoimmune thyroid disease, rheumatoid arthritis was the leading comorbid autoimmune condition but vitiligo was associated as well to a lesser extent [56]. In

Table 1 Comorbid illnesses in vitiligo

	USA (26) [77]	North America/UK (18)	Japan N=133	Iran (7) N=86	Turkey (48) N=80	India (6) N=1010
Atopic dermatitis		N/A				
Alopecia areata	1.8	1.1	5.3		12.5	1.9
Thyroid disease	8.7	17[a]	12	21.1	31	0.7
Rheumatoid arthritis	2.2	0.67				
Psoriasis		1			1.3	0.4
Lichen planus						0.7
Increased fasting blood						
Glucose/diabetes		0.48 (DMI)		4.7	2.5	
Pernicious anemia		1.78		0	8.7	
Ulcerative colitis/IBD	1.7	0.67		0		
Addison		0.38		0		
SLE	1.6	0.19		0		
Low vitamin D levels	>50	N/A				
	55.6 % insufficient (<30 ng/mL)					
	13.3 % deficient (<15 ng/mL) [78]					

[a] 19.4 % for >20 years

children with autoimmune thyroid disease, 2.7 % will have vitiligo [57]. Autoimmune thyroid disease is associated with rheumatoid arthritis [58].

A surface area greater than 25 % was seen in 38.7 % [6]. Nunes notes that the presence of thyroid disease is correlated with a body surface area (BSA) greater than 25 %. In selected populations, consanguinity may affect disease prevalence. A review of 69 patients in Arar, Saudi Arabia (40 males and 29 females), showed 65.2 % had a positive family history (n=45) and 40.6 % had parental consanguinity, with 27.5 % first-cousin consanguinity. Focal type was less associated with family history than acrofacial and universalis [59]. In one study, 20.4 % of patients with vitiligo had a family member with the disease, the mother being the most common (10 %) and the father, sister, or brother (3–3.4 %) [6].

Wang et al. looked at the epidemiology of the Vogt-Koyanagi-Harada disease, the constellation of vitiligo and systemic involvement of the eyes, ears, and meninges, and ocular changes such as bilateral granulomatous panuveitis. Females predominate (60–78 %) in these cohorts, and the disease affects Asian, Hispanic, Native American, and Middle Eastern populations. Male patients are more likely to have chorioretinal detachment. Pregnancy was found to improve the disease [60].

Other comorbidities described include pruritus and photosensitivity with onset before age 30 years [61]. Atopic dermatitis has especially been associated with pediatric vitiligo with onset before age 12 years both in a primary analysis of surveyed patients worldwide and a meta-analysis of combined data including the original trial [62, 63]. Cardiac risk factors are likely less common with vitiligo [64].

Skin Cancer

Generalized vitiligo is associated with a reduced incidence of melanoma and non-melanoma skin cancers in some cases but increases in other studies. The population of patients with vitiligo generally has less photodamage and photoaging. In a population-based survey of over 90,000 Germans, vitiligo was not statistically linked to actinic keratosis development [65]. An inverse association of vitiligo with skin cancer has been noted in patients in Europe (Amsterdam, The Netherlands, and Rome, Italy). Teulings et al. created a postal survey of all patients with generalized vitiligo who had visited their clinic from 1995 to 2010 who were 50 years or older at the time of the survey and their partners. Two thousand six hundred thirty-five patients were mailed a survey and 1307 patients and their partners completed the surveys. Compared to their partners, patients with vitiligo had a threefold lower risk of skin cancers (melanoma adjusted OR 0.32 RR, non-melanoma skin cancer (NMSC) adjusted OR 0.28 RR). The group who had received phototherapy did not have greater incidence; however, this latter finding has been called into question by an Italian study [66].

Hexsel et al. reviewed a cohort of 477 patients with vitiligo and no history of NMSC over approximately 5 years of practice, and a review for onset of NMSC was performed. Six cases were identified and all were Caucasian and over 61 years of age. Age-adjusted incidence rates were for basal cell carcinoma (BCC) in males 1382 per 100,000, 0 for females and for squamous cell carcinoma, 465 per 100,000 males, and 156 per 100,000 females [19]. An Italian group recently reviewed 10,040 patients with vitiligo, comparing them with patients coming in for evaluation for vascular surgery. The crude RR for melanoma was 0.24 (95 % confidence interval (CI) 0.13–0.45) and, for non-melanoma skin cancer (NMSC), the RR was 0.19. The occurrence rate of 3.8 % (95 % CI 2.7–5.2 %) of NMSC in vitiligo as compared to 19.6 % (95 % CI 18.0–21.4 %) in controls was reported. These rates are surprisingly low given the overall usage of phototherapy in the vitiligo patients; however, the authors noted a marked increase in skin cancer risk for melanoma and NMSC patients than vitiligo patients not treated with phototherapy exposure [19]. Nine thousand five hundred forty-three had not had phototherapy and 497 had phototherapy. The relative risk without phototherapy was 0.17 and with phototherapy 0.34 for NMSC, with melanoma occurring in only 8 vitiligo patients who had not had phototherapy and in 3 of the 497 patients who had phototherapy. The relative risk of NMSC was 4.67 and 7.54 for melanoma for phototherapy over no phototherapy in vitiligo [19]; despite these facts, the adjusted risk was felt to be 0.3.

Psychological Comorbidity

Psych comorbidity is often high with 60 % reporting in a Serbian cohort of children and adolescents. Age-based data from Silverberg et al. demonstrates that psychological comorbidity including reduced quality of life and increasing self-consciousness rises consistently with age from smaller children up through adolescent ages 15–17 years [67]. In a cohort of 308 patients, 54.5 % experienced depression, mostly mild and correlated to age, sex, and marital status; skin phototype was correlated in another study as well [68, 69]. Psychological comorbidities can extend to family members, with one study showing over 90 % experiencing a negative effect on their quality of life [70]. Silverberg has demonstrated that pruritus, abdominal cramping, and facial location may become predictors for psychiatric disease and for risk of bullying. Extent is associated with quality of life impairments of adults and itching. Vitiligo of the genitalia is associated with poorer quality of life and sexual dysfunction (18 %). Other risk factors for poorer quality of life are being younger, being single, low income, and long disease duration [71]. Anxiety may also be

noted in patients with vitiligo and is the second leading psychiatric comorbidity [72].

Factors Impacting Disease

The presence of atopic dermatitis may also confer a greater risk of BSA greater than 25 % [73, 74]. Other risk factors for BSA greater than 25 % are being born in the USA and living farther from the equator. There was an inverse relationship of latitude and disease severity [75]. This may have to do with vitamin D levels in early childhood, Western diet, and/or ongoing UV stimulation. The fact that vitiligo cases are rare in early childhood in the desert region further corroborates this issue [6]. Poor response to therapy was noted in that study with family history of vitiligo [7].

The presence of low vitamin D levels (<15 ng/mL) in vitiligo noted in 13.3 % of a New York, NY, cohort from Silverberg et al. has been linked to greater risk of secondary autoimmunity (e.g., thyroid disease, diabetes). Therefore, screening for low levels and appropriate supplementation per Institute of Medicine guidelines may be beneficial to the vitiligo patient's overall health [76].

Conclusions

The epidemiology of vitiligo worldwide has similar prevalence; however, it is clear that we do not have a full understanding of the reasons for differences in prevalence, sex distribution, and environmental contributory factors. Worldwide genome-wide association studies may reveal reasons for these differences as well. Large-scale collaborative epidemiologic studies may reveal differentiating factors in disease onset, severity, and prevalence.

Compliance with Ethics Guidelines

Conflict of Interest NB Silverberg declares no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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