Is there a correlation between vitiligo and hearing loss? - review of the literature

Barbara Rusinowska

Student Research Group at the Chair and Department of Epidemiology and Clinical Research Methodology; Medical University of Lublin

Contact: rusinowskabarbara4@gmail.com; +48 794303542

Orcid: 0000-0002-8207-1042

Abstract

Vitiligo is the most common cause of hypopigmentation occurring with a frequency of 0.5-2% relying on impairment of melanin production caused by the loss of melanocytes. Melanocytes are observed not only in the skin's epidermis and hair follicles but also in the mucosa, the uvea, mesencephalon and on the structures of inner ear – including the stria vascularis, the cochlea and the dark cell areas in the vestibular organs where they play role in regulation auditory and equilibrium functions. These rationale prompted scientists to study the link between hearing loss and vitiligo. Scientists' opinions are divided in this respect - some of them, as a result of their research, see a possible connection, others do not see a correlation between the two diseases. In this review, we present the latest studies evaluating the correlation of hearing impairment with vitiligo.

Keywords: vitiligo; hearing loss; melanocytes; Waardenburg syndrome; SNHL
Introduction

Vitiligo is the most common cause of hypopigmentation occurring with a frequency of 0.5-2% relying on impairment of melanin production [1]. The disease is characterized by the appearance of discolored, hypopigmentation patches, usually symmetrical on both sides, caused by the loss of melanocytes. The spots are clearly marked, of various sizes, and can occur anywhere on the skin, but most often around the mouth and eyes, neck, straight surfaces of the limbs, backs of the hands, in the armpits, around the natural openings of the body, rarely on the mucous membranes. It may happen that hypopigmentation spots appear in places of injuries (Koebner's symptom). Depending on the location, there are limited (focal and segmental) vitiligo, generalized (acra-facial and common) vitiligo, total and mixed vitiligo [2]. Along with vitiligo, other diseases can coexist - diabetes, thyroid disease, Addison's disease, sickle cell anemia, as well as early graying of hair, Sutton nevus, psoriasis, lichen planus and alopecia areata [2,3].

Melanocytes are localized not only in the skin's epidermis and hair follicles but also in the mucosa, the uvea, mesencephalon and on the structures of inner ear [4]. In the inner ear, melanocytes are observed in the stria vascularis, in the cochlea and the dark cell areas in the vestibular organs, where they play the role of hemolymph homeostasis and that way regulate auditory and equilibrium functions. Destruction of melanocyte in inner ear can lead to its dysfunction. Studies made by van Beelen et al. showed that before 7 week of embryogenesis vestibular melanocytes are localized around the utricle and the ampullae in the inner ear. Melanocytes in the saccule were not observed in any of the developmental stages of the inner ear during embryogenesis [5,6].

Waardenburg syndrome (WS) is rarely group of genetic disorders caused by abnormal distribution of melanocytes during embryogenesis. Patchy hypopigmental areas in skin, hair, eyes, stria vascularis of the cochlea are effect of loss of melanocytes in this disease. There are four types of WS. Type I (due to mutations in the PAX3 – autosomal dominant) is characterised by sensorineural congenital deafness, dystopia canthorum, neural tube defects, cleft palate, cleft lip and depigmentation of skin and hair. Type 2 (due to mutations in the MITF – autosomal dominant and in SNAI2 – autosomal recessive) manifests without dystopia of inner canthorum but is similar than in type 1 of WS with milder pigment anomalies and heterochromia. Type 3 (due to mutations in the PAX3 – autosomal dominant) also known as Klein-Waardenburg syndrome coexist with malformations of upper limbs, broad nasal root, hearing loss and depigmentation. Type 4 of WS is also called as Waardenburg-Shah syndrome with depigmentation and hearing loss and has two subtypes. Type 4A caused by mutations in SOX10, EDN3, EDNRB is autosomal dominant type with coexisting constipation. Type 4B arises as a result of autosomal recessive mutations in EDN3, EDNRB. This type coexists with Hirschsprung disease with high risk of aganglionic megacolon [7,8,9].

The mechanism of the disease has not been fully elucidated. It is suspected that genetic and immunological factors, innervation disorders, microvascular anomalies, oxidative stress and the related melanocyte degeneration, somatic mosaicism and melanocyte adhesion disorders may play a role in the pathogenesis of vitiligo [10]. The detection of antimelanocyte antibodies in immunofluorescence in the 1970s in people with vitiligo confirms the large role of the autoimmune mechanism in the development of the disease [10,11]. The immune response in vitiligo is assumed to be humoral and cellular immunities.
T lymphocytes are involved in the autoimmune pathomechanism of localized-type of vitiligo, and the role of T lymphocytes and NK cells in the pathomechanism of the diffuse form. In people genetically burdened with vitiligo, overexpression of the B-lymphocyte activating factor is observed, which may lead to the self-activation of B-lymphocytes to produce autoantibodies against melanocytes. The autoimmune reaction is additionally enhanced by the interactions of CD4+ and CD8+ T cells. A patchy infiltration of CD8+ T cells is observed near the melanocytes. Moreover analysis by Chen et al. showed that the increased level of these lymphocytes increases the destruction of melanocytes, while their decrease reduces the progression. CD8 + T cells release INF-γ, which further enhances the activity and accumulation of CD8 + lymphocytes, increasing the immune response, and INF-γ itself exerts a cytotoxic effect on melanocytes. Increased expression of programmed cell death protein-1 (PD-1), T-cell immunoglobulin and mucin-domain on the CD8 + surface in patients with vitiligo has also been demonstrated [11,12]. Circulating antinuclear antibodies (ANA) are also seen in some patients with vitiligo [13]. The studies of El-Gayyar et al. showed increased titers of ANA, AMA and C4 antibodies in patients with vitiligo compared to the control sample of healthy patients. The level of C3 does not seem to be of significant importance - no differences were found between the two groups in the study. The results also showed a correlation between disease activity and AMA antibody titer, which is important in the mechanism of cytotoxicity and possibly also antigen uptake and presentation by dendritic cells [11]. The research of Kroon et al. showed no correlation between antibodies against melanocytes concentration and vitiligo activity [14]. However, although the autoimmune hypothesis seems to be the most correct, the coexistence of many factors in the pathogenesis of the vitiligo cannot be ruled out [11].

In this review, we present studies evaluating the correlation of hearing impairment with vitiligo.

**Scientific research results**

There are many studies looking at the correlation between vitiligo and hearing loss. Reserches made by Prabha et al. examined the effect of vitiligo on audiological functions. Otological examination were checked in 52 patients with vitiligo (28 men and 24 women; mean age was 26.7 years) from January 2017 to July 2017 in the hospital. Pregnant women, people taking ototoxic drugs, people exposed to chronic noise, people with family hearing loss, people with previously diagnosed otological problems, people with vascular, neurological and systemic diseases were excluded from the study. Otological examination included external examination, tuning fork and pure tone audiometry also with air and bone conduction thresholds. Of these patients, ten (19.2%) had sensorineural hearing loss (SNHL) - seven (13.5%) had bilateral SNHL, and 3 (5.7%) had unilateral SNHL. Most SNHL were detected in the age group 41 to 60 years old. SNHL was observed in 5 out of 10 patients (66.7%) in vitiligo period under 5 years and 5 out of 32 (86.5%) – vitiligo period above 5 years. In these 10 patients, loss of high frequencies occurred in 17 out of 20 ears. 6 ears had a defect in high and low frequencies. The results of Prabha studies suggest routine monitoring for auditory functions in patients with vitiligo which will allow for earlier identification of hearing disorders (SNHL) and implementation of treatment.
A greater exposure to audiological disturbances has been observed in older patients. In addition, vitiligo patients should avoid noise and ototoxic drugs [15]. Sheng-Hsiang et al. reached similar conclusions - regular audiologic assessment is indicated in patients with vitiligo in order to detect hearing disorders earlier. In addition, research by Sheng-Hsiang et al. has linked vitiligo to SNHL [16]. Studies made by Li et al. also shown an increased risk of SNHL in patients with vitiligo. The cohort study included 3048 vitiligo patients and 52192 controls, adjusted for age (the mean age in study group with vitiligo was 42.61; the mean age in controls was 42.63), sex (43% participants were men in both groups) and comorbidities (a very similar percentage of people in both groups had hypertension, diabetes, hyperlipidemia, peripheral vascular disease, coronary artery disease, cerebrovascular disease and diffuse connective tissue diseases). Development of SNHL was observed in 0.61% of vitiligo patients and 0.29% of controls. A significant correlation was found between vitiligo and the incidence of SNHL in almost all subgroups – results of the study showed increased risk of SNHL by 2.2-fold in patients with vitiligo, particularly in people over the age of 50. Scientists emphasize the important role of hearing screening in patients with vitiligo, especially in the elderly [17].

Studies by Arya et al. compared the audiological and otological functions in patients with vitiligo with the normal controls and investigated the effect of vitiligo duration on audiological disorders. The study was conducted in 50 patients (25 women and 25 men) aged 11-50 years with a mean age of 27.4 years. 16 patients was diagnosed with localized vitiligo and 34 with generalized vitiligo. 23 people had a duration of vitiligo of less than 60 months and 27 were more than 60 months. People used ototoxic drugs in the past, people with previously diagnosed otological problems and middle ear disorders, people with vascular, neurological, metabolic and systemic diseases were excluded from the study. The control group consisted of 40 people who were matched for age, sex, otology and audiology. The audiological assessment in the conducted study included pure tone audiometry (PTA), high frequency audiometry, otoacoustic emissions (OAEs) - distortion product OAEs (DPOAEs) and transient evoked OAEs (TOAEs), tympanometry, auditory brainstem response audiometry (ABR), middle latency responses (MLR). In the research group at low frequencies (PTA1), most people had normal hearing (right ear - 49, left ear - 48). In PTA2, among 100 ears, there was a mild hearing loss in three and a moderate hearing loss in four ears. In PTA3, with extended high frequencies per 100 ears, a mild hearing loss was detected in 16, in 30 - moderate, 26 - severe, 3 - profound. DPOAEs was not observe in 12 people in right ear and 14 people in left ear in study group. TOAE were absent in 28 patients in right ear and 25 patients in left ear. Results of the studies showed higher PTA2 in generalized vitiligo in comparison to localized vitiligo. Include duration on audiometry in vitiligo was most significant in PTA2 – patients with longer history of vitiligo had worse hearing thresholds. Results presented high frequency hearing loss of cochlear origin in people with vitiligo. Researchers believe that it is possible to correlate hearing disorders with the presence of vitiligo, but confirmation requires further research on a larger group of people [18].
Manno et al. investigated audiological abnormalities and potential vestibular injury in patients with vitiligo. The study involved 35 patients with non-segmental vitiligo (NSV) and carried out them pure tonal audiometry (PTA) – for checking auditory performance; vestibular Fitzgerald-Hallpike caloric test, C-VEM, O-VEMP (to investigate any possible vestibular involvement). The PTA result showed bilateral hearing loss in 69%, unilateral hearing loss in 8%, and normal hearing in 23%. Bilateral caloric stimulations caused unilateral pathological response in 14% and bilateral pathological response in 9%. 20% of patients did not respond to O-VEMP and 3% did not respond to C-VEMP. Comparing the VEMP score in NSV patients to healthy patients showed a 44% difference in the study. Scientists suspect that hearing degeneration may be related to NSV. In addition, they recommend performing bithermal caloric testing, C-VEMP and O-VEMP, even in asymptomatic individuals, to assess vestibular damage [19].

Rahimi et al. tested hearing loss in patients with vitiligo by audiometry and distortion product otoacoustic emission (DPOAE) to determine the link between these two diseases. 53 people with vitiligo and 52 controls matched for sex (the ratio of women to men in study group was 33:20 and 39:13 in controls) and age (the mean age in study group was 35.09; in controls – 39.63) participated in the study. The mean duration of vitiligo was 9.57 years. All participants underwent otological and audiological examinations including pure tone audiometry (PTA) and DPOAE. The results showed no significant differences in both studies conducted in the study and control group in frequencies 0.75-8 KHz. In addition in study group no correlation between PTA and DPOAE studies was observed between age, sex, positive family history of vitiligo, duration of vitiligo, type and vitiligo occupancy. According to scientists, there is no link between vitiligo and hearing loss but it requires large, multicentre studies to confirmed this thesis [20].

Moghaddam et al. checked the correlation between skin involvement intensity and hearing loss intensity among patients with vitiligo. The study was conducted on a group of 98 people with vitiligo with the mean age of 25.98 years, most patients were women – 68.4%, in whom dermatologists assessed skin involvement by the disease (VASI index), and then audiological tests were carried out (audiometry, tympanometry and auditory brainstem response - ABR). Patients with congenital hearing impairment and those taking ototoxic drugs in the past were excluded from the study. Conductive hearing loss was observed in 9 patients (9.2%), in turn neural hearing loss was detected in 4 patients (1.4%). Scientists found no relationship between skin involvement and hearing impairment. In addition, there was no association of vitiligo with SNHL and no association of disease duration with conductive and sensory neural hearing loss. However, scientists, as well as other teams, believe that further, more numerous and cohort studies should be carried out to assess the audiological assessment of patients with vitiligo [6].

**Conclusion**

While the presence of melanocytes in the inner ear suggests a possible hearing loss in vitiligo patients, there is no clear evidence linking vitiligo to hearing loss. The presented studies may indicate the correlation of vitiligo with hearing impairment, but this thesis requires more numerous, cohort, multi-center and multi-ethnic studies with a larger group of patients, which many scientists emphasize.
References


