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Prevalence of Impaired Hearing and Vision in Patients with Vitiligo

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ABSTRACT Vitiligo is a common dermatosis occurring with a frequency of about 0.2-4.0% in world population. The main skin symptom of disease are white patches appearing as a result of destruction or dysfunction of pigment cells (melanocytes). Melanocytes are localized not only in epidermis and bulge region of hair follicle, but also in inner ear and eyeball structures, and therefore vitiligo may coexists with auditory and visual disorders. The most frequent auditory and visual disturbances occurring in vitiligo patients are discussed in this article.

KEY WORDS: vitiligo, hearing, vision.

INTRODUCTION

Vitiligo is a systemic idiopathic disease characterized by the presence of sharply demarcated, discolored spots caused by epidermal melanocyte loss or damage. This disease affects all races equally regardless of sex, with an incidence of 1% to 2%. The first descriptions of the disease are found in ancient Indian guides, the Old Testament, and the Koran. Many types of vitiligo have been identified: localized, including focal and segmental, and generalized, including acrofacial, vulgaris, and universal (1,2). The mechanism underlying the spots in vitiligo is not completely understood, although many theories of the disease etiology have been postulated. The most popular of these include autoimmune, auto-cytotoxic, and neurogenic mechanisms. The autoimmune theory is based on the coexistence of vitiligo with autoimmune diseases, often preceded by the signs of Sutton disease, and skin melanoma. In 1% to 3% of patients with melanoma, foci of hypopigmentation, depigmentation, or discoloration develop around halo nevi (3). The latest theories involve viral apoptotic, adhesion, and multifactorial disorders.

A number of studies have explored the genes responsible for the development of vitiligo, includ-

ing acetylcholinesterase, major histocompatibility complex, chloramphenicol transferase, cytotoxic T-lymphocyte associated protein 4, catechol-O-methyltransferase, estrogen receptor, guanosine triphosphate cyclohydrolase I, mannose binding lectin 2, protein tyrosine phosphatase non-receptor type 22, and vitamin D3 receptor (4). In patients with vitiligo and other autoimmune disorders, Jin *et al*. (5) located the NALP1 gene on the short arm of chromosome 7, which encodes a protein rich in leucine, a primary regulator of the immune system. The hypothesis relating vitiligo to neurogenic mechanisms originated from observations of segmental vitiligo in areas designated by the dermatomes, and in association with adrenergic orthostasis or altered metabolism of acetylcholine and adrenergic neurotransmitters. The autoimmune and neurogenic theories are also supported by the presence of the Koebner phenomenon in generalized vitiligo (6, 7). Twenty-four hours after mechanical injury, non-specific migration of melanocytes occurs. The auto-cytotoxic hypothesis is based on the observation that phenol and some of its derivatives are toxic to melanocytes, and can produce a chemical leucoderma. Tyrosinase, a key enzyme involved in melanin biosynthesis from phenol and some of its precursors, can produce free radicals and destroy melanocytes (8).

A cytomegalovirus genome has been identified in the epidermal cells of patients with vitiligo (9). Patients with hepatitis C viral infection, acquired immune deficiency syndrome, and human immunodeficiency virus carriers have an increased incidence of vitiligo (10-14). The hypothesis assumes that apoptotic destruction of melanocytes is the mechanism of programmed cell death due to weakening of the protective signaling pathway, SCF (ckit) MIFT/Bcl2. The apoptotic process of melanocytes is exacerbated by the weakening of the expression of the gene encoding Bcl-2.

Normal interactions between melanocytes and the basement membrane require alpha-beta 1 integrin. Interactions between melanocytes and keratinocytes occur through the actions of beta-catenin and cadherin (14). Repetitive bending of joints with unaltered skin in patients with vitiligo results in peeling and transepidermal elimination of melanocytes. This theory also explains the occurrence of positive Koebner symptoms in the active form of the disease (15).

The multifactorial theory assumes that vitiligo occurs primarily in genetically predisposed patients exposed to a variety of adverse environmental factors. The etiology of vitiligo, unfortunately, remains unclear, and the disease has many clinical forms. According to the latest multifactorial theory, exogenous or endogenous phenols that are a competitive substrate for tyrosine are present in the microenvironment of pigment cells. Due to an imbalance in reduction and oxidation, competitive substrates are transformed into reactive quinones. Tyrosinase metabolizes quinones to products that may represent new antigens. The newly formed antigens are presented by Langerhans cells in the regional lymph nodes, which leads to cytotoxic T cell proliferation. Finally, cytotoxic T lymphocytes and macrophages migrate into the skin and destroy melanocytes (16-18).

The diagnosis of vitiligo is based on clinical presentation and is generally quite easy. Secondary studies for the diagnosis of discrete changes are performed by Wood's lamp examination. The Wood's lamp highlights the contrast between the properly colored skin and the vitiligo patch. Although vitiligo is not directly life-threatening, this disease can be a source of serious psychological problems and lead to social isolation (19).

Vitiligo coexists with autoimmune diseases and visual and auditory disorders. In patients with vitiligo, discoloration of the eyelids and loss of eyelashes and eyebrows are frequently observed. Moreover, eye uveitis and, less frequently, discoloration of the iris, atrophy of the retinal pigment epithelium (RPE), and other retinal disorders, such as discoloration and/or increased pigmentation of the eye fundus, are observed in patients with vitiligo. Vitiligo is also associated with auditory and balance disturbances (20).

AUDITORY MANIFESTATIONS OF VITILIGO

The target tissues for the distribution of melanocytes are not only the epidermis and hair, but also the mucosa of the ear, eye, and mesencephalon (21). In the ear, melanocytes are located in the stria vascularis as intermediate cells, where they modulate the function of Na+/K+ -ATPase and potassium channels, which are essential for creating the endocochlear electrical potential (22). The electrical activity of ciliary cells in the labyrinth is closely connected with their physiological ability to send afferent information to brain areas involved in auditory and balance functions.

Opinions vary on hearing loss associated with melanocyte destruction. Lin *et al*. (23), analyzing 1258 adults, suggested an association between darker skin and better hearing on the basis of subjective hearing tests. Because skin pigmentation is the marker of melanocyte function, it is reasonable that vitiligo may be associated with disturbances of the inner ear (which contains melanocytes). Moreover, destruction of the epithelium is often coexistent in the inner ear and retina (24).

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Several studies report impaired hearing following disruption of melanin synthesis, melanosome structure, or their distribution (25). None of these studies, however, have examined the site of damage that leads to hearing impairment, which can be the cochlea as well as the upper part of the auditory system, as seen in retinitis pigmentosa coupled with axonal polyneuritis followed by hearing loss (26). Melanocytes are also distributed in the mesencephalon, which is a part of the hearing pathway.

Ardic *et al*. (27) noted lower pure tone thresholds at higher sound frequencies (from 4000 – 16,000 Hz) in patients with vitiligo. Based on their observations, as well as the fact that social and environmental damage affects hearing at the same sound frequencies, the authors suggested a preventive role of melanocytes (and melanin-containing cellular elements) for the sensitive inner ear cells. Sensorineural hypoacusis was reported also by Sharma *et al*. (28) in ~10% patients with vitiligo, but the conductive type of hearing loss was detected in 8% of this group. Aydogan *et al*. (29) observed that patients with vitiligo have disturbances in the upper part of auditory pathway, in cranial nerve VIII, and above the level of the cochlear nuclei in the pons. The frequency of hypoacusis was similar to that in previous reports and affected ~14% of 57 tested patients. Among Korean patients with vitiligo, hearing loss was confirmed to be connected with cochlear damage as objective electrocochleography revealed increases in summation and action potentials of auditory cells in the labyrinth (30). The use of otoacoustic emissions seemed to confirm the pathology of the cochlear cells, especially at 4000 Hz (31). Moreover, successful cochlear implantation in patients with auditory symptoms concurrent with autoimmune destruction of melanocytes might be the evidence for cochlear localization of hearing injury related to vitiligo (32).

Some reports, however, do not support a connection between hearing loss and vitiligo. Escalante-Ugalde *et al*. (33), Ozuer *et al*. (34), and Al-Mutairi *et al*. (35) observed no correlation between hypoacusis and vitiligo, even in a large group of 197 patients. Gopal *et al*. (36) suggested that the hearing loss could result from other diseases coexisting with vitiligo, such as diabetes mellitus and hypothyroidism. In fact, as vitiligo is reported to be of systemic origin, autoimmune-associated diseases could be responsible for the observed hypoacusis. Akay *et al*. (37) reported that 55% of patients with vitiligo have autoimmune diseases. Abad *et al*. (38) emphasized the role of self-antigens originating from melanocytes, but a search for targeted melanocytic proteins in patients with multisystemic autoimmune diseases of tissues containing melanin in the eye, inner ear, meninges, and skin was unsuccessful.

Several issues remain to be solved regarding vitiligo and the associated impairment of sensory organs. First, there is a clear connection between hearing loss and melanocyte disease; second, the localization of the auditory pathway injury; and third, the coincidence of auditory and balance system destruction in some clinical cases of vitiligo.

OCULAR MANIFESTATIONS OF VITILIGO

Depigmentation of the eyelid and poliosis of the eyebrows and eyelashes are often observed in vitiligo (39). In addition to the skin, melanocytes are found in the leptomeninges, retinal pigment epithelium (RPE), the uveal tract, and the inner ear. Typically, melanocyte abnormalities in the eyes and ears are asymptomatic and not observed by physicians, but their involvement in vitiligo is well established and in some cases can be related to severe ocular diseases. There are two populations of pigment-bearing cells in the eye: the uveal melanocytes, which are morphologically similar to dermal melanocytes, and the RPE (40). Melanocytes present in the choroid are responsible for constitutive eye pigmentation and protection against ultraviolet (UV) radiation. These cells are important for the degradation of toxic factors (41). The association of vitiligo with inflammation of the uveal tract is well established. Clinical manifestations of acute uveitis in patients with vitiligo were observed in 8% of 112 patients (42). Biswas *et al*. reported the symptoms of uveitis in only 5% of a group of 100 patients (43). Wagoner *et al*. reported a 4.8% incidence of uveitis in a group of 223 patients with vitiligo and 5.4% incidence of cutaneous depigmentation in a group of 129 patients with uveitis of an unknown cause (44).

Vitiligo is associated with pigmentary changes in the fundus of the eye. The RPE is formed by a distinct type of melanocytes as the outermost layer of the retina. These melanocytes are involved in the metabolism of retinoids and rod outer segments, and play a major role in vision (41). Although melanocyte abnormalities in the fundus of the eye are usually asymptomatic, they occur frequently. Wagoner *et al*., in a study of 223 patients with vitiligo, reported chorioretinal scars and RPE hypopigmentation in 30% of the patients or RPE atrophy in 27% of the patients (44). Cowan *et al*. detected some degree of fundal pigment disturbance in 40% of 156 patients with vitiligo (45). Different types of fundal pigment disturbances are linked to vitiligo, such as pigment clumps, focal hypopigmented spots, diffuse hypopigmentation,

diffuse, focal, or sectoral atrophy of the RPE, or chorioretinal scars (42,46). Some researchers have observed ring-like peripapillary atrophy around the optic nerve (39). There are some isolated reports of vitiligo occurring with tapetoretinal degeneration (47,48). Retinitis pigmentosa and retinitis pigmentosa-like syndromes are seen sporadically in patients with vitiligo, and patients with vitiligo more often complain of night blindness, but the relationship between vitiligo and retinitis pigmentosa is difficult to assess (42,46).

Vitiligo is associated with many primarily autoimmunologic disorders. Vitiligo is strongly associated with uveal inflammation in Vogt-Koyanagi-Harada disease, a systemic autoimmune disorder that affects pigmented tissues of the body, with the most severe manifestations in the eyes. Patients with Vogt-Koyanagi-Harada disease can present with early acute uveitic manifestations (i.e. bilateral diffuse choroiditis with bullous serous retinal detachment and optic disc hyperemia) and late ocular manifestations (i.e. diffuse fundus depigmentation, nummular depigmented scars, retinal pigment epithelium clumping and/or migration, and recurrent or chronic anterior uveitis), in addition to extraocular manifestations (neurologic/auditory and integumentary) (49).

The connection between the anatomic localization of vitiligo and ocular findings was primarily investigated by Rosenbaum *et al*. (50), who reported an association between bilateral changes in the RPE with periorbital vitiligo and seizures. Other researchers have come to similar conclusions. Wagoner *et al*. suggested that periocular skin depigmentation is a frequent abnormality in patients with ocular findings (44). Baskan *et al*. reported that ocular findings are primarily associated with periorbital and, to a lesser extent, genital vitiligo (39).

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