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The relationship between risk factor and clinical type of vitiligo in dermatology and venerology outpatient clinic Dr. Soetomo General Academic Hospital Surabaya

Alvian Arifin Saiboo

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Diah Mira Indramaya

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Afif Nurul Hidayati

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Rahmadewi

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Damayanti

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Cita Rosita Sigit Prakoeswa

Department of Dermatology and Venereology, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Academic Hospital, Surabaya, Indonesia
Corresponding author email: cita-rosita@fk.unair.ac.id

Abstract--Vitiligo is a skin and mucosa depigmentation condition caused by the loss of functioning melanocytes. Various pathological mechanisms are involved in melanocytes, their full details are often difficult to explain and several risk factors for vitiligo are thought to play a role. This study describe the relationship between risk factors and clinical type of vitiligo. This study is an analytic observational study with a retrospective cross sectional design based on the medical records patients who were treated in Dermatology and Venerology Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya.

The result of this study found 115 new vitiligo patients with the following characteristics were female (53.9%), late adolescence (26.96%) and students (25.22%). The most common risk factors were idiopathic (51.3%) and emotional (28.7%). The most common clinical type was non-segmental vitiligo (53.04%). There was relationship between emotional and the clinical type of vitiligo ($p=0.023$ $p<0.05$) and there was relationship between idiopathic risk factors and the clinical type of vitiligo ($p=0.019$ $p<0.05$). There was relationship between emotional risk and idiopathic factors with the clinical type of vitiligo that were related to pathogenesis becomes important to understand to identify therapeutic targets and prognostic implications to stop the progression of the disease.

Keywords--Vitiligo, risk factors, clinical type, treatment, human and disease.

Introduction

Vitiligo is a depigmentation disorder of the skin and mucosa, resulting from the loss of functional melanocytes (Yuan et al., 2019). Vitiligo has a complex etiology and varies in manifestation, development, and response to treatment (Soepardiman, 2011). The prevalence of vitiligo is estimated to be between 0.5-2% worldwide and epidemiology in Indonesia is not yet clear in detail (Yuan et al., 2019). Retrospective data of vitiligo in Dermatology and Venerology Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya in 2012-2014 was still high although there was a slightly decrease (Rahmawati et al., 2016; Prasetya et al., 2019).

The increase in cases of vitiligo cannot be separated from the precipitating factors in this disease. A variety of pathological mechanisms are involved in the loss of melanocytes in vitiligo, and their full details are often difficult to explain (Jeonet et al., 2014; Bilal et al., 2016; Bergqvist et al., 2020). The international consensus classifies vitiligo into two main forms, namely non-segmental vitiligo and segmental vitiligo (Ezzedine et al., 2012).

This study aimed to evaluate the relationship between risk factors and clinical type in vitiligo patients. The results of this study are expected to be able to provide information on risk factors that play a role in the incidence of vitiligo and clinical types in vitiligo patients, so that as a Dermatologist is able to detect clinical vitiligo patients, provide education and optimal therapy so that it is expected to help reduce morbidity in vitiligo patients.

Method

This study is an analytic observational study with a retrospective cross sectional design based on the medical records of vitiligo patients who were treated at Cosmetics Division in Dermatology and Venerology Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya in 2018 - 2020. The inclusions criteria were all of the patients recorded in medical records with a clinical diagnosis of vitiligo

at Cosmetic Division in Dermatology and Venereology Outpatient Department Dr. Soetomo Surabaya for the period of 2018 - 2020.

Those data inputed into a data collection sheet to be analyzed using the Statistical Package for Social Sciences (SPSS). This research has obtained ethical approval from the Ethics Committee of Dr. Soetomo General Academic Teaching Hospital Surabaya (0892/LOE/301.4.2/IV/2022).

Result

The results of this study obtained 115 new patients with vitiligo, who were treated at Cosmetics Division in Dermatology and Venerology Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya in 2018 - 2020 with the characteristics the most of gender is female (53.9%), the most of age group is late adolescence (17-25 years) (26.96%), and the most of the patient's occupations are students (25.22%) which could be seen in table 1. In table 2, showed relationship risk factor and clinical type of vitiligo patients

Table 1 Demographic distribution of vitiligo patients

Variable	Total (n=115)
Gender, n (%)	
- Male	53 (46.1)
- Female	62 (53.9)
Age (years,n(%))	
- 0 - 5	8 (6.96)
- 6 - 11	8 (6.96)
- 12 - 16	5 (4.35)
- 17 - 25	31(26.96)
- 26 - 35	9 (7.83)
- 36 - 45	15 (13.04)
- 46 - 55	23 (20)
- 56 - 65	12 (10.43)
- > 66	4 (3.48)
Occupation, n (%)	
- Housewife	21 (18.26)
- Student	29 (25.22)
- Teacher	4 (3.48)
- Private / BUMN employees	18 (15.65)
- PNS/TNI/POLRI	2 (1.74)
- Self-employed	23 (20)
- Laborer	2 (1.74)
- Farmer	1 (0.87)
- Driver	2 (1.74)
- Not yet working	13 (11.30)

Table 2. Evaluation of the relationship risk factor and clinical type of vitiligo patients

Risk factors	Clinical type	n	p
Family/genetic history	Segmental	5 (9.3)	0.116
	Non-Segmental	12 (19.7)	
Emotional factors	Segmental	10 (18.5)	0.023
	Non-Segmental	23 (37.7)	
Physical trauma	Segmental	3 (5,6)	0.261
	Non-Segmental	7 (11.5)	
Systemic disease	Segmental	2 (3,7)	0.074
	Non-Segmental	8 (13.1)	
Autoimmune disease	Segmental	1 (1.9)	0.127
	Non-Segmental	5 (8,2)	
Idiopathic	Segmental	34 (63.0)	0.019
	Non-Segmental	25 (41.0)	

Discussion

This retrospective study found a total of 115 new patients with vitiligo who were treated at Cosmetics Division in Dermatology and Venerology Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya in 2018 - 2020. The most gender distribution of vitiligo patients was female (53.9%) than male (46.1%). The results of this study are the same as the previous study by Rahmayanti, which reported that female vitiligo patients visited more than men, namely 68.1% with a female to male ratio of 2.1:1 (Rahmayanti, 2016). Vitiligo is widely considered to have an autoimmune basis, and gender equality is generally not uncommon among autoimmune diseases (Aboul-Fettouh et al., 2018). Women usually tend to notice changes in the pigmentation of their skin and its impact on cosmetics, especially when vitiligo lesions appear on the face, so women may seek treatment more often.

The most age group of patients was 17-25 years, which was 31 patients (26.96%), then 46-55 years by 23 patients (20%). The youngest age group 0-5 years had 8 patients (6.96%) and the oldest age group above 66 years had 4 patients (3.48%). This result was different from the research by Rahmayanti, the most vitiligo patients were in the 25-44 year age group, which was 32.3% (Rahmayanti, 2016). Age distribution in new patients with vitiligo can facilitate the choice of therapy, such as in pediatric patients and elderly patients should be careful in topical corticosteroid therapy about the risk of increased the drug absorption (Jorge et al., 2020).

The distribution of the occupation of the most vitiligo patients was student (25.22%), self-employed (20%) and housewife (18.26%). The results of this study are the same as those conducted by Dwiyananda and colleagues at Dr. Hasan Sadikin Bandung Hospital, who reported that the majority occupations of vitiligo patients were students (30.99%) and housewife (21.49%) (Dwiyananda et al., 2017). The data about the occupation of new vitiligo patients mentioned above were less meaningful because they are unable to explore factors that could trigger the onset

of vitiligo in patients. However, from the research results, the majority occupations of the patients in this study were indoor which were less to direct sun exposure, but students could have other outdoor activities related to hobbies such as sports.

In this study, the risk factors vitiligo patients at Cosmetics Division in Dermatology and Venerology Outpatient Clinic Dr. Soetomo General Academic Hospital Surabaya in 2018 – 2020 is an idiopathic factor (51.3%), emotional (28.7%), family history of vitiligo / genetic (14.8%), systemic disease (8.7%), history of physical trauma (8.7%), and autoimmune disease (5.2%). Vitiligo is a multifactorial inherited disease with a polygenic pattern Alkhateeb et al., 2003). This theory is in accordance with this study, it was found that some vitiligo patients had more than one risk factor so that it was analyzed in a multifactorial manner.

In this study, idiopathic risk factors are the most common risk factors for vitiligo. According to Listiawan's study, which was some of the difficulties in dealing with vitiligo patients are the vitiligo disease itself, which has a very complex pathogenesis and its complete pathogenesis that could not be explained (Listiawan, 2017). Vitiligo is characterized by the appearance of white macules due to loss of epidermal melanocytes caused by cell damage through melanocyte-specific cytotoxic immune responses and release of melanocytes through the defective adhesion system. The multiple mechanisms involved in the loss of melanocytes do not adequately explain all parts of this complex skin disorder (Boniface et al., 2017). It was not clear why melanocytes stop producing melanin and what risk factors trigger it.

Emotional risk factors are the second most common risk factor in this study. Vitiligo lesions show elevated norepinephrine levels, and decreased parasympathetic acetylcholine esterase activity. Increased neurotransmitters may be directly cytotoxic to cells, or they may have an indirect effect through local vasoconstriction leading to hypoxia and then stress-generated hydrogen peroxide (H₂O₂). There is evidence that this neural dysregulation is systemic and that vitiligo often occurs during periods of increased stress (Morrone et al., 1992). Emotional could increase levels of neuroendocrine hormones that affect the immune system and alter neuropeptide levels. Emotional could stimulate the secretion of catecholamines, which could bind to alpha receptors in the skin and on the arteriolar mucosa, causing vasoconstriction, hypoxia, and overproduction of oxygen free radicals that destroy melanocytes, through stimulation of the hypothalamic-pituitary-adrenal axis (Malhotra et al., 2013).

In this study, there was a statistically significant relationship between several risk factors for vitiligo and the clinical type of vitiligo, including idiopathic risk factors ($p < 0.05$, test *Chi-Square*) and emotional risk factors ($p < 0.05$, test *Chi-Square*). The pathogenesis of vitiligo is complex and has not been fully elucidated. Both the innate and adaptive immune systems also appear to be involved in the pathogenesis of vitiligo. No single theory has been proposed that suffices to explain the different phenotypes of vitiligo, and the overall contribution of each of these processes is debated although there is currently a known consensus about

the autoimmune nature of vitiligo. Several combined pathological mechanisms may be involved in the progressive loss of melanocytes (Bergqvist et al., 2020).

Idiopathic risk factors in the clinical type of segmental vitiligo (63%) are more than that of non-segmental vitiligo (41%). Statistically there is a significant relationship ($p < 0.05$, test *Chi-Square*) between idiopathic risk factors and the clinical type of vitiligo. The same risk factor mechanism may not apply in all cases, and different pathogenetic mechanisms may cooperate (convergence or integrated theory), ultimately leading to the same clinical outcome. With recent advances, understanding risk factors in the pathogenesis of vitiligo is very important and a challenge for dermatologists.

The risk factors for stress / psychic / emotional in the clinical type of non-segmental vitiligo (37.7%) were more than that of segmental vitiligo (18.5%). This difference was statistically significant ($p < 0.05$, test *Chi-Square*). The relationship between stress and clinical types of vitiligo is still being studied. Psychological stress increases levels of neuroendocrine hormones that affect the immune system and alter neuropeptide levels. Elevated levels of neuropeptides are an early event in the pathogenesis of vitiligo (Parsad et al., 2003).

In individuals who are susceptible to vitiligo, it leads to activation of the immune system resulting in a melanocyte-specific cytotoxic response. Heat shock protein (HSP) is a cellular stress response protein that protects cells under stress conditions. Notably, among the HSP family, inducible HSP70 (HSP70i) is secreted by living cells under stress. It was reported that HSP70i from melanocytes in accelerating autoimmune vitiligo. Stressed cells secrete HSP70i and in the extracellular environment, HSP70i could activate dendritic cells (DCs) and aid in antigen cross-presentation, resulting in a cytotoxic T cell response to melanocytic antigens (Han Shen et al., 2020). The exact role of stress in the pathogenesis of vitiligo and the relationship between stress and the development of various types of vitiligo lesions should be clarified by prospective studies with a clinical and immunoserological focus.

The risk factors for autoimmune disease in patients with non-segmental type of vitiligo (8.2%) were higher than the clinical segmental type (1.9%). However, this difference was not statistically significant ($p > 0.05$, test *Chi-Square*). This seems to be related to the asymptomatic clinical manifestations of autoimmune disease so that the patient is not aware of any disease other than the vitiligo lesion. Currently, the autoimmune/inflammatory theory was the predominant hypothesis because vitiligo is often associated with autoimmune disease, the loci of vitiligo susceptibility best identified through genomic association studies encoding immunomodulatory proteins, and prominent immune cell infiltrates at the perilesional margin of actively depigmented skin (Boniface et al., 2017). The autoimmune hypothesis is supported by the observation that several autoimmune diseases often coexist with vitiligo. The most commonly reported autoimmune diseases were autoimmune thyroid disorders, diabetes, pernicious anemia, and alopecia areata (Szezurko et al., 2011).

Non-segmental vitiligo, especially vitiligo vulgaris, is the clinical type most likely to have the strongest genetic control. A recent family-based study conducted in

the same population demonstrated that there is an association between vitiligo and a genetic marker of the Discoidin Domain Receptor 1 (DDR1) gene, which encodes an important mediator of melanocyte adhesion to the basement membrane, an effect that may be concentrated in cases non-segmental vitiligo (de Castro et al., 2010). In non-segmental vitiligo had risk factor from family history (Ongenaes et al., 2005). This result is the same as this study, family risk factors for vitiligo non-segmental (19.7%) than vitiligo segmental (9.3%). However, this difference was not statistically significant ($p > 0.05$, test *Chi-Square*).

Segmental vitiligo often exhibits features that help differentiate it from vitiligo vulgaris, such as a low frequency of family history and autoimmune disease. Khaitan and colleagues reported the same thing that the incidence of family history and autoimmune disorders was lower in segmental vitiligo compared to non-segmental vitiligo (Khaitan et al., 2012). This suggests that autoimmunity may not be an important pathway for the pathogenesis of segmental vitiligo. Convergence theory states that chemical accumulation, infection, autoimmunity, mutation, altered cell environment, and impaired melanocyte migration can all contribute to the pathogenesis of vitiligo. Exposure to chemicals acting as tyrosine analogues were taken up by melanocytes, interact with tyrosinase, and induce cellular stress pathways that then activate immune inflammation to initiate or exacerbate vitiligo (Ezzedine et al., 2012). The accumulation of chemicals also cause an increase in the production of Reactive Oxygen Species (ROS). Disruption and accumulation of ROS can have toxic effects on all cell components and potentially result in melanocyte damage, creating depigmented macules. Oxidative stress in vitiligo most likely exerts a pro-inflammatory effect and has melanocyte-damaging capacity in vitro (Speeckaert et al., 2018).

In this research, the risk factors for physical trauma in vitiligo non-segmental (11.5%) more than in vitiligo segmental (5.6%). This difference was not statistically significant ($p > 0.05$, test *Chi-Square*). Although various environmental factors that could influence the development of vitiligo could be encountered in everyday life, in many cases, the initiation of aggravating factors and causes has not been clearly identified.

The relationship between systemic disease and the development of vitiligo may be explained according to neurohumoral theory. The neurohumoral theory asserts that depigmentation in vitiligo is the result of increased release of certain substances at peripheral nerve endings in the skin (eg, melatonin) that lighten pigments and reduce the formation of new melanin. Nervous system dysregulation, either at the local or systemic level could damage the melanocytes in vitiligo. To support this, both melanocytes and nerves arise from neural crest cells, and some vitiligo was segmental vitiligo, follows neural distribution, and exhibits alterations in perspiration and changes in neural structure (Orecchia GE, 2000).²⁵ In this research, the risk factors for systemic disease in non-segmental vitiligo more (13.1%) than in segmental vitiligo (3.7%). This difference was not statistically significant ($p > 0.05$, test *Chi-Square*). There has been no research related to the correlation between risk factors for systemic disease and the clinical type of vitiligo.

Conclusion

The conclusion there was the relationship between idiopathic and emotional risk factors with the clinical type of vitiligo. It could be concluded that the relationship of vitiligo with several risk factors indicates that knowledge and understanding of the pathogenesis was important. Disease mechanisms may identify novel therapeutic targets that could halt disease progression and promote cell regeneration thereby stimulating repigmentation in the affected area of vitiligo. Improved therapeutic and diagnostic modalities will substantially improve patient compliance and satisfaction.

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