Acta Derm Venereol 2015; 95: 169–172

INVESTIGATIVE REPORT

Autonomic Nervous Tone in Vitiligo Patients – A Case-control Study

Eva-Maria TRAPP[1], Michael TRAPP[2], Francesca SAMPOGNA[3], Peter Michael ROHRER[2], Josef Wilhelm EGGER[2], Peter WOLF[4], Hans-Peter KAPFHAMMER[1], Michael Dennis LINDER[5], Erika RICHTIG[4], Johannes BAULMANN[6] and Angelika HOFER[4]

Departments of [1]Psychiatry, [2]Medical Psychology and Psychotherapy, Research Unit of Behavioural Medicine, Health Psychology and Empirical Psychosomatics and [4]Dermatology, Medical University of Graz, Graz, Austria, [3]Health Services Research Unit, Istituto Dermopatico dell'Immacolata (IDI)-IRCCS, Rome, [5]Department of Dermatology, University of Padua, Padua, Italy, and [6]Medizinische Klinik II, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Lübeck, Germany

In this cross-sectional, exploratory case-control study the vegetative arousal in vitiligo patients compared to an age- and gender-matched healthy control group was assessed. Forty-eight participants (24 outpatients with generalised vitiligo and 24 healthy controls) completed a test procedure consisting of an initial period of rest (R1), a defined mental stress task (the d2 test of attention), a second period of rest (R2) followed by an individually, age-adapted physical stress task (bicycle ergometry) and a final period of rest (R3). Based on a continuously recorded electrocardiogram, heart rate variability, in particular high frequency (HF) and low frequency (LF) components were determined. Within the 3 periods of rest, vitiligo patients showed a higher vegetative arousal than controls, represented by the ratio of LF/HF which mirrors the sympatho-vagal balance (R1: $p=0.027$; R2: $p=0.003$; R3: $p=0.029$). No differences between the 2 groups were found during the mental ($p=0.187$) and the physical stress task ($p=0.773$). The results suggest a higher vegetative arousal in vitiligo patients. ***Key words: vitiligo; autonomic nervous tone; vegetative arousal; sympatho-vagal balance; mental and physical stress.***

Accepted May 12, 2014; Epub ahead of print May 13, 2014

Acta Derm Venereol 2015; 95: 169–172.

Eva-Maria Trapp, Department of Psychiatry, Medical University of Graz, Auenbruggerplatz 31/1, AT-8036 Graz, Austria. E-mail: eva.trapp@medunigraz.at

Two major forms of vitiligo are generally described: generalised and segmental (1, 2). Generalised vitiligo (GV) is an acquired skin disorder in genetically predisposed subjects, characterised by depigmented patches in the skin due to a progressive loss of active melanocytes from the epidermis.

GV usually presents with white patches in a symmetrical distribution on mechanically distressed area like the elbows, knees, hands and feet but can also occur around the eyes and mouth and in the genital region. The worldwide prevalence is 1%, and 50% of vitiligo patients show clinical signs of the disease before the age of 20 years. Though GV itself appears to present no direct "organic" health risk, it is often associated with diseases of the thyroid gland (35%), diabetes mellitus I (DM I), Addison's disease, alopecia areata and other autoimmune diseases (3–5). Also, nearly one quarter of vitiligo patients reported that the quality of their personal life is severely reduced due to the disfigurement (6).

The exact aetiopathology of vitiligo has not been established yet, however the main pathomechanisms seem to be autoimmune reactions against melanocytes and self-destruction of melanocytes due to damaging factors (7). Neuropeptides and catecholamine released from the epidermal nerve fibres in stress situations are examples of such damaging factors and it is not surprising that progressive periods of vitiligo often occur after episodes of mental stress (8).

Several studies showed that plasma catecholamine and metabolites were elevated in vitiligo patients and that vitiligo patients had significantly more stressful life events at the onset of their disease than controls (9–11).

Indeed the experience of uncontrollable events, low social support and the inability to cope with stress seem to trigger vulnerability and susceptibility to vitiligo (12, 13). Vitiligo is also strongly associated with a reduced quality of life (QoL) (14–16), where women appear to be more emotionally affected than men (17–19). Therefore it seems beneficial to offer psychological support in addition to the medical treatment of vitiligo (20–22).

Heart rate variability (HRV) is a commonly used psycho-vegetative parameter that mirrors the functioning of the autonomic nervous system (ANS) (23). Using specific analysis methods of HRV, the low frequency (LF) band is a strong indicator of sympathetic activity, and the high frequency (HF) component reflects parasympathetic tone. Thus, the ratio LF/HF indicates the balance between sympathetic and parasympathetic activity (23).

The aim of this study was to assess the autonomic nervous tone during different standardised conditions (*i*) at rest, (*ii*) during a mental stress task and (*iii*) during a physical stress task in GV patients as compared to age- and gender-matched controls who were not affected by a skin disease.

MATERIAL AND METHODS

Patients

Patients and controls were contacted between April 2008 and February 2011 and were enrolled in the study at the Department

© 2015 The Authors. doi: 10.2340/00015555-1896

of Dermatology, Medical University of Graz. Twenty-four outpatients, 16 women and 8 men (mean age 39.6 years) with GV were assigned to the vitiligo group and were compared with an age- and gender-matched control group of 24 subjects, 16 women and 8 men (mean age 40.1 years). All participants were Caucasians and all patients of the vitiligo group were affected by GV with a mean disease duration of 7.79 years (range from 1–21 years). In 19 patients (79.2%) vitiligo was in progression, in 5 patients (20.8%) vitiligo was stable. Further information of the study sample are given in Table SI[1].

Inclusion criteria: Age between 18 to 75 years, sufficient knowledge of the German language, understanding of the tasks to be performed and declared interest in taking part in the study, in the presence of hypothyroidism (e.g. Hashimoto's thyroiditis) adequate treatment.

Exclusion criteria: On-going treatment with steroids, phototherapy or immune-therapy.

As HR and HRV are modulated by internal and external factors, the following exclusion criteria were defined in order to ensure the validity of the data: not adequately treated diabetes mellitus, arrhythmias, arterial hypertension, diseases of the thyroid gland other than hypothyroidism and beta blocker therapy as well as a body mass index >30 kg/m^2.

Participants were asked in advance to abstain from the consumption of nicotine, caffeine and alcohol 3 h before the test procedure.

All institutional rules governing clinical investigations of human subjects were strictly followed during the study. The study was conducted in accordance with the human medical experimentation ethics document (Declaration of Helsinki 1964 and subsequent revisions). Approval was obtained from the local ethics committee. Anonymity was guaranteed by identifying each participant with an ID number.

Physiological methods

During the test procedure participants were continuously monitored with ECG using the measurement system Task Force® Monitor (CNSystems, Graz, Austria). Based on the ECG HRV in particular the components LF normalised units (nu) and HF HFnu (23) were calculated and their ratio (LF/HF), reflecting sympatho-vagal balance (23–25), was determined. Normalised units (nu) of LF and HF components represent the balance between sympathetic and parasympathetic tone (23). A higher LF/HF ratio indicates increased sympathetic tone or reduced parasympathetic tone and thus an increased activation of the ANS (23).

Test procedure

Participants completed a baseline questionnaire about socio-demographic and medical data, including age, sex, education, family status, medication regarding the thyroid gland and smoking behaviour (see Table SI[1]). Subsequently, the participants performed a defined test procedure. Single steps of the test procedure are shown in Fig. 1.

Periods of rest

The periods of rest R1 (6 min), R2 (6 min) and R3 (10 min) were performed in a sitting position with closed eyes.

Mental stress task – d2 test of attention

The standardised test "d2" (26) is used as an attention test with "p's" and "d's", in total 658 characters, within 14 rows and with

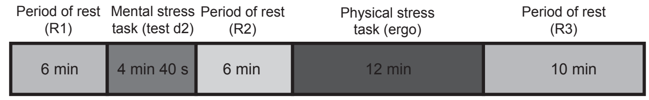

Fig. 1. Sequence of the test procedure.

47 letters per row. Every "p" and "d" has a number of vertical lines on the top, below or on both sides, with a maximum of 4 lines per letter. Participants were asked to work as fast as they could to sign each "d" with 2 dashes and to ignore all "p´s" and all "d´s" with less or more than 2 dashes. Twenty seconds were allowed for each row, thus the maximal processing time was 4 min and 40 s. The test "d2" is a frequently used test in Europe to measure mental and visual concentration.

Physical stress task

The participants performed a physical stress task (ergo), which was adapted individually to the age of every participant. The individual physical limit was calculated using a standardised age-related norm table (0.75 W/kg for 6 min) and was then held at a constant level of 65% of the maximum age-related HR for a further 6 min. A bicycle ergometer was used in order to perform the defined ergotropic stress task.

Statistical analysis

The median values of each cardiac parameter, HR, LFnu, HFnu and the ratio of LF/HF at each time point (R1, d2, R2, ergo and R3) in vitiligo patients and in controls were compared using the non-parametric Mann-Whitney test.

Linear regression models with a cardiac parameter as the dependent variable and age, sex and "group" (case/control) as independent variables were tested to see if the association between the cardiac variable and the "group" was still significant after adjusting for the other variables.

RESULTS

The median values of the cardiac parameters (HR, LFnu, HFnu and LF/HF), which were significantly different in vitiligo patients and controls are shown in Table I. The parameter HFnu was higher in controls than in vitiligo patients at R1 ($p=0.043$), R2 ($p=0.003$) and R3 ($p=0.035$). HR was always higher in vitiligo patients than in controls except for time "ergo" (R1: $p=0.004$; d2: $p=0.037$; R2: $p=0.019$; R3: $p=0.034$). LF/HF ratio and LFnu median values were higher in vitiligo patients than in controls at R1 (LF/HF ratio: $p=0.027$; LFnu: $p=0.043$), R2 (LF/HF ratio: $p=0.003$; LFnu: $p=0.003$) and R3 (LF/HF ratio: $p=0.029$; LFnu: $p=0.035$).

Further analysis using a linear regression model with HR at time R1, d2, R2 and R3 (HR at ergo was not calculated, because HR was held at a constant level) as the dependent variable and age, sex and "group" (case/control) as independent variables, showed that the association between HR and "group" was still significant after adjusting for other variables. The variable "group" was still significant for the variables HFnu and LFnu as well, both at time R2 and R3. On the other hand, the effect of "group" was no longer significant for the variable LF/HF ratio when adjusting for age and sex.

[1]https://doi.org/10.2340/00015555-1896

Table I. *Median values, minimum and maximum values of the cardiac parameters in vitiligo patients and controls*

	R1	d2	R2	ergo	R3
HR, bpm					
Vitiligo	**76.9, 54.2–76.9**	**85.4, 59.5–120.3**	**76.4, 54.2–100.5**	113.9, 102.6–141.2	**80.2, 55.8–108.3**
Control	**69.2, 53.1–84.2**	**79.4, 52.6–105.0**	**71.1, 52.2–84.0**	114.8, 98.0–131.8	**74.6, 56.8–86.7**
LFnu					
Vitiligo	**69.9, 29.9–96.5**	66.9, 30.7–80.4	**68.9, 29.0–93.0**	56.0, 21.1–89.9	**69.9, 25.6–89.1**
Control	**57.7, 16.8–92.3**	57.1, 13.8–92.8	**53.4, 17.0–94.7**	52.0, 24.3–89.3	**56.2, 18.6–95.3**
HFnu					
Vitiligo	**30.1, 3.5–70.1**	33.1, 19.6–69.3	**31.0, 7.0–71.0**	43.9, 10.1–78.9	**30.1, 10.9–74.4**
Control	**42.2, 7.7–83.2**	42.9, 7.2–86.2	**46.6, 5.3–83.0**	48.0, 10.7–75.7	**43.8, 4.7–81.4**
LF/HF ratio					
Vitiligo	**3.0, 0.4–50.6**	2.2, 0.4–6.3	**2.7, 0.4–29.5**	1.5, 0.3–14.4	**2.9, 0.4–12.7**
Control	**1.4, 0.2–18.2**	1.4, 0.2–16.0	**1.3, 0.2–29.9**	1.1, 0.3–10.0	**1.5, 0.2–30.7**

Bold figures indicate $p<0.05$ for the Mann–Whitney test. R: rest periods; d2: test of attention; ergo: physical stress task.

DISCUSSION

In the periods of rest vitiligo patients showed a higher vegetative arousal than healthy controls, represented by the ratio of LF/HF, LFnu, HFnu and HR. However, this effect was neither present during mental stress (except HR) nor during the ergotropic phase.

The parameter LFnu, which predominantly represents sympathetic and partly parasympathetic components (23, 24), was significantly higher in vitiligo patients as compared to controls. Additionally, the parasympathetic tone, reflected by the HFnu component (23, 24) is reduced in vitiligo patients. Both findings indicate clearly sympathetic dominance and thus, higher vegetative arousal in patients who suffer from vitiligo. Due to the fact that this study was conceptualised as a cross-sectional exploratory study, we can merely state that patients who suffer from vitiligo, have a higher vegetative arousal compared to healthy controls. Based on the present results with the given study design, however, no statements can be made in terms of aetiology and pathogenesis. A study involving a larger number of individuals should be envisaged, since this could allow stratification and data analysis in subgroups with satisfactory statistical power of the results, e.g. patients with stable vitiligo vs. patients with vitiligo in progression might (or might not) show different autonomic response, and the same might be true for patients with different duration of disease. In recent years, a convincing body of studies has been published which present the concept of HRV based determination of sympatho-vagal balance using the LF/HF ratio (23, 25). However, there are indeed critical approaches to the concept of sympatho-vagal balance (27). A recently published article by Billman (28) highlights the vulnerability of the LF/HF concept, indicating a variety of variables that can influence sympathetic and parasympathetic activity.

Based on the available data we cannot state whether the increased vegetative arousal caused the genesis and progress of the disease, or whether the burden of being diagnosed with vitiligo leads to the hyper-arousal. Obviously, vitiligo patients show an increased vegetative arousal as measured by the LF/HF ratio based on HRV. However, a possible cytotoxic effect of catecholamines and their catabolites (e.g. o-diphenol) is thought to be associated with the aetiopathogenesis of vitiligo (29, 30). Studies reported higher catecholamine and metabolite levels at the onset and during the early phase of vitiligo, which possibly mirrors an increased activity of the monoaminergic systems probably induced by psychosocial stress (10).

In other skin diseases, we know that shame plays an important role as an additional stressor which can promote the exacerbation of specific dermatological diseases (e.g. psoriasis) (31, 32). The disfigurement, which is caused by skin diseases like vitiligo and psoriasis lead to high levels of experienced stigmatisation and shame (32, 33). The feeling of being stigmatised again potentially causes high levels of psycho-social stress and has considerable impact on the patients' QoL especially on an emotional level (16, 34), a state which again can be associated with a higher vegetative arousal.

Considering the importance of the regulation of our emotions, we should take into account the permanent interaction between the different systems, namely the tight connection between the limbic system, the hypothalamus, the endocrine system, the autonomic system and the immune system (35, 36). The limbic system, as a centre of our emotions, is functionally associated with the hypothalamus, which modulates the endocrine system and the autonomic nervous system and subsequently influenced by different pathways, it also modulates the immune system (37).

In conclusion, on a physiological level we found significant differences between vitiligo patients and unaffected controls, indicating a higher vegetative arousal in vitiligo patients. Thus we can hypothesise that vitiligo patients suffer higher levels of strain and may profit from a multidimensional therapeutic intervention which implements strategies that aim to reduce the autonomic nervous tone. Behavioural interventions, relaxing training and strengthening the individual resilience in order to achieve higher stress tolerance could be considered to be effective ways to reduce individual arousal and to improve the QoL of patients with vitiligo.

ACKNOWLEDGEMENTS

We would like to thank Thorsten Weissenböck, MD for assisting in patient recruitment and Prof. Günther Schwaberger for counseling in sports physiology.

REFERENCES

1. Dell'anna ML, Picardo M. A review and a new hypothesis for non-immunological pathogenetic mechanisms in vitiligo. Pigment Cell Res 2006; 19: 406–411.
2. Taieb A. Intrinsic and extrinsic pathomechanisms in vitiligo. Pigment Cell Res 2000; 13 Suppl 8: 41–47.
3. van Geel N, Speeckaert M, Brochez L, Lambert J, Speeckaert R. Clinical profile of generalized vitiligo patients with associated autoimmune/autoinflammatory diseases. J Eur Acad Dermatol Venereol 2014; 28: 741–746.
4. Narita T, Oiso N, Fukai K, Kabashima K, Kawada A, Suzuki T. Generalized vitiligo and associated autoimmune diseases in Japanese patients and their families. Allergol Int 2011; 60: 505–508.
5. Kumar S, Mittal J, Mahajan B. Colocalization of vitiligo and alopecia areata: coincidence or consequence? Int J Trichology 2013; 5: 50–52.
6. Kostopoulou P, Jouary T, Quintard B, Ezzedine K, Marques S, Boutchnei S, et al. Objective vs. subjective factors in the psychological impact of vitiligo: the experience from a French referral centre. Br J Dermatol 2009; 161: 128–133.
7. Schallreuter KU, Bahadoran P, Picardo M, Slominski A, Elassiuty YE, Kemp EH, et al. Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else? Exp Dermatol 2008; 17: 139–140; discussion 41–60.
8. Namazi MR. Neurogenic dysregulation, oxidative stress, autoimmunity, and melanocytorrhagy in vitiligo: can they be interconnected? Pigment Cell Res 2007; 20: 360–363.
9. Salzer BA, Schallreuter KU. Investigation of the personality structure in patients with vitiligo and a possible association with impaired catecholamine metabolism. Dermatology 1995; 190: 109–115.
10. Cucchi ML, Frattini P, Santagostino G, Orecchia G. Higher plasma catecholamine and metabolite levels in the early phase of nonsegmental vitiligo. Pigment Cell Res 2000; 13: 28–32.
11. Papadopoulos L, Bor R, Legg C, Hawk JL. Impact of life events on the onset of vitiligo in adults: preliminary evidence for a psychological dimension in aetiology. Clin Exp Dermatol 1998; 23: 243–248.
12. Picardi A, Pasquini P, Cattaruzza MS, Gaetano P, Melchi CF, Baliva G, et al. Stressful life events, social support, attachment security and alexithymia in vitiligo. A case-control study. Psychother Psychosom 2003; 72: 150–158.
13. Manolache L, Benea V. Stress in patients with alopecia areata and vitiligo. J Eur Acad Dermatol Venereol 2007; 21: 921–928.
14. Ongenae K, Van Geel N, De Schepper S, Naeyaert JM. Effect of vitiligo on self-reported health-related quality of life. Br J Dermatol 2005; 152: 1165–1172.
15. Sampogna F, Raskovic D, Guerra L, Pedicelli C, Tabolli S, Leoni L, et al. Identification of categories at risk for high quality of life impairment in patients with vitiligo. Br J Dermatol 2008; 159: 351–359.
16. Kim do Y, Lee JW, Whang SH, Park YK, Hann SK, Shin YJ. Quality of life for Korean patients with vitiligo: Skindex-29 and its correlation with clinical profiles. J Dermatol 2009; 36: 317–322.
17. Radtke MA, Schafer I, Gajur A, Langenbruch A, Augustin M. Willingness-to-pay and quality of life in patients with vitiligo. Br J Dermatol 2009; 161: 134–139.
18. Borimnejad L, Parsa Yekta Z, Nikbakht-Nasrabadi A, Firooz A. Quality of life with vitiligo: comparison of male and female muslim patients in Iran. Gend Med 2006; 3: 124–130.
19. Karelson M, Silm H, Kingo K. Quality of life and emotional state in vitiligo in an Estonian sample: comparison with psoriasis and healthy controls. Acta Derm Venereol 2013; 93: 446–450.
20. Papadopoulos L, Bor R, Legg C. Coping with the disfiguring effects of vitiligo: a preliminary investigation into the effects of cognitive-behavioural therapy. Br J Med Psychol 1999; 72: 385–396.
21. Wong SM, Baba R. Quality of life among Malaysian patients with vitiligo. Int J Dermatol 2012; 51: 158–161.
22. Nogueira LS, Zancanaro PC, Azambuja RD. [Vitiligo and emotions]. An Bras Dermatol 2009; 84: 41–45 (in Portugues).
23. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996; 93: 1043–1065.
24. Perini R, Veicsteinas A. Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. Eur J Appl Physiol 2003; 90: 317–325.
25. Ori Z, Monir G, Weiss J, Sayhouni X, Singer DH. Heart rate variability. Frequency domain analysis. Cardiol Clin 1992; 10: 499–537.
26. Brickenkamp R, Zillmer E. d2 Test of Attention. Göttingen, Germany: Hogrefe & Huber, 1998.
27. Eckberg DL. Sympathovagal balance: a critical appraisal. Circulation 1997; 96: 3224–3232.
28. Billman GE. The LF/HF ratio does not accurately measure cardiac sympatho-vagal balance. Front Physiol 2013; 4: 26.
29. Morrone A, Picardo M, de Luca C, Terminali O, Passi S, Ippolito F. Catecholamines and vitiligo. Pigment Cell Res 1992; 5: 65–69.
30. Orecchia G, Frattini P, Cucchi ML, Santagostino G. Normal-range plasma catecholamines in patients with generalized and acrofacial vitiligo: preliminary report. Dermatology 1994; 189: 350–353.
31. Sampogna F, Tabolli S, Abeni D, investigators IDIM-PRoVE. Living with psoriasis: prevalence of shame, anger, worry, and problems in daily activities and social life. Acta Derm Venereol 2012; 92: 299–303.
32. Hrehorow E, Salomon J, Matusiak L, Reich A, Szepietowski JC. Patients with psoriasis feel stigmatized. Acta Derm Venereol 2012; 92: 67–72.
33. Thompson AR, Clarke SA, Newell RJ, Gawkrodger DJ; Appearance Research Collaboration (ARC). Vitiligo linked to stigmatization in British South Asian women: a qualitative study of the experiences of living with vitiligo. Br J Dermatol 2010; 163: 481–486.
34. Schmid-Ott G, Kunsebeck HW, Jecht E, Shimshoni R, Lazaroff I, Schallmayer S, et al. Stigmatization experience, coping and sense of coherence in vitiligo patients. J Eur Acad Dermatol Venereol 2007; 21: 456–461.
35. Egger JW. Biopsychosocial Medicine. Psychologische Medizin 2012; 23: 45–49.
36. Havelka M, Lucanin JD, Lucanin D. Biopsychosocial model – the integrated approach to health and disease. Coll Antropol 2009; 33: 303–310.
37. Kemeny ME, Schedlowski M. Understanding the interaction between psychosocial stress and immune-related diseases: a stepwise progression. Brain Behav Immun 2007; 21: 1009–1018.