

CLINICAL REPORT

Higher Psychological and Psychovegetative Strain in Adolescents with Atypical Pigment Naevi

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An observational, exploratory, cross-sectional study was performed to assess whether the presence of atypical naevi (AN) in adolescents is associated with psychological and psychovegetative stress parameters. Fifty-one students of a secondary school in Graz, Austria, completed a defined test procedure consisting of an initial period of rest, a standardised mental stress task, another period of rest and a questionnaire, the change-sensitive symptom list (ASS-SYM). Electrocardiogram and blood pressure were recorded continuously. The study population was divided in two groups: probands without AN (NAN, $n=33$), and probands with at least one AN ($n=18$). We found higher values for the AN group in all scales of ASS-SYM, reaching statistical significance in the dimensions “nervousness and mental tension” ($p=0.025$), “psychophysiological dysregulation” ($p=0.020$), “burden of pain” ($p=0.023$) and “general symptoms and problems” ($p=0.031$). Regarding physiological parameters, the AN group showed higher vegetative strain reflected in heart rate and heart rate variability during the periods of rest as well as a reduced baroreceptor sensitivity. On the basis of our results, the presence of AN in adolescents seems to be associated with a higher vegetative arousal. Additionally, participants with AN complained significantly more often about stress-associated general psychological symptoms and problems. *Key words: atypical pigment naevi; adolescence; mental stress; biopsychosocial melanoma research.*

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Naevogenesis is a complex process leading to the appearance of naevi on the skin. During embryogenesis melanoblasts (immature melanocytes) leave the neural crest and migrate to the skin, forming nests in the dermis and proceeding further to the epidermis. A dual pathway of naevogenesis has been presented with an endogenous

pathway, genetically determined, and an exogenous pathway due to UV radiation (1). Naevi arising via the endogenous pathway are brownish macules or papules built predominantly by dermal melanocytes with globular or cobblestone pattern in dermoscopy and a stable life cycle (1–4). The exogenously arising naevi seem to have a dynamic life cycle with predominantly epidermal melanocytes with reticular pattern in dermoscopy and mostly macular appearance at onset (1). A third pathway has been discussed recently in considering the possible role of growth-related hormones (4): thus, an onset of eruptive naevi has been observed after immunosuppression, treatment with α -melanocyte hormone or during pregnancy (5, 6).

Before puberty dermal naevi with a globular pattern are the most frequent naevi revealing mostly compound melanocytic tumours in histopathology. In adults, junctional naevi with a reticular pattern in dermoscopy are predominantly showing junctional melanocytic nests in the rete ridges in histopathology (3). In early adolescence and around puberty mixed patterns are observed with peripheral globules in dermoscopy (4). Whereas acquired melanocytic naevi arise on the skin after the age of 6 months, mostly in the first 2 decades of life, atypical or dysplastic naevi may manifest from childhood till late adulthood, mostly observed, however, around puberty (2). Prevalence of atypical naevi reported in the literature vary between 2% and 20% – 1.5% in children (7) (cited in (8)). Those atypical naevi are defined as naevi with at least 3 of the following clinical features: diameter ≥ 5 mm, ill-defined border, irregular margin, varying colour within the lesion and papular and macular components (9). Atypical naevi count is described to be a very relevant risk factor for melanoma (10). In marathon runners it was shown that higher physical strain is associated with a higher number of naevi (11). Also mental stress can induce strain depending on individual resilience factors (12) and influences physiological processes modulated by the autonomic nervous system (13). The fact that every psychological phenomenon needs to be associated to a physiological process is increasingly gaining accep-

tance (14). Thus psychosocial/emotional and chronic stress can be associated with an increased output of the hypothalamus-pituitary adrenal (HPA) axis as well as the sympathetic nervous system (12, 13, 15) resulting in specific dysregulations, such as an increase in norepinephrine levels and glucocorticoids, heart rate (HR), blood pressure (BP), reduction of heart rate variability (HRV) and baroreceptor control (16–19). The low frequency (LF) component of HRV reflects sympathetic and to a certain extent parasympathetic activity (20, 21). In contrary, high frequency (HF) component of HRV reflects the parasympathetic tone (20, 21). Thus the ratio LF/HF mirrors the sympatho-vagal tone (20–22). A reduction in baroreceptor sensitivity (BRS) is associated with a decreased parasympathetic outflow to the heart (19). We hypothesised that psychological variables (“general symptoms and problems”, parameters of the change-sensitive symptom list; ASS-SYM), i.e. “physical and psychological exhaustion”, “nervousness and mental tension”, “psychophysiological dysregulation”, “performance and behavioural problems”, “burden of pain”, as well as “self-determination and self-control problems” could be considered as risk factors for mental stress that again can be associated with a higher physiological arousal. In the present exploratory study we investigated to what extent the presence of atypical naevi in adolescents is linked to co-existing psychological and psychovegetative parameters, both considered as factors of mental strain.

MATERIALS AND METHODS

Fifty-one students of a secondary school in Graz, Austria, were enrolled in the study. The students were informed by their teachers, the headmaster of the secondary school and the investigators of the study. They were provided the relevant information about the study both in written and in oral form. They had to provide the informed consent form signed by their parents or legal guardian (if under 14 years) and additionally by themselves (if older than 14 years). All volunteers fulfilled the following inclusion criteria: age between 12 and 16 years, enough compliance and command of the German language to fill out the questionnaires and complete the test d2. Before the start of the test procedure all participants were informed about the test sequence and the possibility to stop at any time without giving a reason. The Declaration of Helsinki was strictly followed during the study. Anonymity was warranted by each participant given an ID number.

When all participants' questions concerning the design of the study had been answered the electrodes/sensors for the measurement of psychophysiological parameters were applied.

The test procedure (Fig. 1) was performed under standardised conditions and consisted of: 1) Period of rest in sitting position with closed eyes (R1, duration: 5 min); 2) Mental task (d2 test of attention, duration: 4 min and 40 s); 3) Period of rest in sitting position with closed eyes (R2, duration: 5 min); 4) Completion

of the ASS-SYM; and 5) Skin examination (performed not earlier than one week after the test procedure).

d2 test of attention

The d2 test is a standardised paper-pencil attention and concentration assessment measuring processing speed, quality of performance and rule compliance. It consists of 14 rows containing the letters *p* and *d*, (each row comprises 47 letters, total 658 characters) with 1–4 dashes attached (either individually or in pairs above and below the letter respectively). The participants are asked to tick off only the letters *d*, which are accompanied by exactly 2 dashes regardless of their positions. Participants have to ignore all *p* as well as *d* with less or more than 2 dashes. For a single row, the participants are given 20 s time before they had to proceed. In order to ensure precise progress and to standardise the signal to change to the subsequent row an mp3-file was created. The d2 test is a widely used and well validated psychometric instrument (23–28).

Change-sensitive symptom list – ASS-SYM

The ASS-SYM¹ (Change-sensitive symptom list in respect of relaxation, well-being, complaints and problems) is a standardized validated psychometric questionnaire analysing general symptoms and problems (29, 30). It is composed of 48 items arranged in 6 subscales: “physical and psychological exhaustion”, “nervousness and mental tension”, “psychophysiological dysregulation”, “performance and behavioural problems”, “burden of pain” as well as “self-determination and self-control problems”. The tested individuals are asked to respond to each item by declaring to what extent a defined discomfort, problem, emotion or thought appeared within the past 14 days (i.e. never, rarely/sometimes, frequently/moderately, very often/more pronounced). The ASS-SYM can be filled out without time limitation, but usually takes less than 15 min. During the first 3 parts of the test procedure (R1, d2 test of attention, R2) electrocardiogram (ECG) and BP were measured non-invasively and recorded continuously with Task Force[®] Monitor (CNSystems, Graz, Austria). For BP measurement double finger sensors measured the signal continuously that was calibrated to oscillometric values of BP. Based on physiological measurements ECG and BP, the psychovegetative parameters (HR, BP, BRS and ratio LF/HF) were calculated with implemented TFM software, which uses an adaptive autoregressive parameter (AAR) algorithm (31) for calculating HRV (LF/HF) and the Sequence-Method to estimate the BRS (32, 33). After completion of the test procedure the amount and presence of naevi – atypical naevi, respectively – were assessed in all participants by a single certified dermatologist of the Department of Dermatology and Venereology, Medical University of Graz. Atypical naevi were defined as naevi with at least 3 of the following clinical features: diameter ≥ 5 mm, ill-defined border, irregular margin, varying colour within the lesion and papular and macular components (9). According to the outcome of the dermatological examination, participants were assigned either to the atypical naevi group (AN) or to the group without atypical naevi (NAN).

¹In German: Änderungssensitive Symptomliste zu Entspannungserleben, Wohlbefinden, Beschwerden- und Problembelastungen

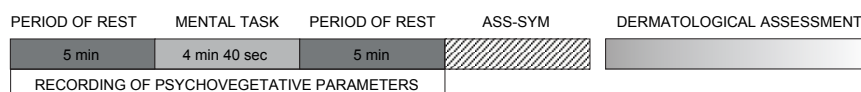


Fig. 1. Sequence of the test procedure.

Statistical analysis

For all ASS-SYM scales we explored the data in each patient group (AN and NAN) and for all psychovegetative parameters we explored the data in each measurement (R1, d2 and R2) for each group using the Shapiro-Wilk test. We decided to rely on non-parametric statistics since at least one group (or one of the 6 group*measurement divisions, respectively) differed significantly from a normal distribution.

Wilcoxon rank sum test was used to assess group differences among AN and NAN.

As a multivariate analysis for changes in the psychovegetative data during the sequence of the test procedure (R1, d2, R2) within both groups we used a non-parametric repeated measures analysis on ranks (Friedman test) as global testing procedure with Wilcoxon signed ranks tests as *post hoc* tests to assess which measurement pairs differ. For *post hoc* tests we adjusted the significance level for multiple comparisons according to Bonferroni and we report the corrected *p*-values. A *p*-value of 0.05 or less was considered as statistically significant.

All computations were performed with the statistical software package IBM SPSS Statistics (Release 19.0.0. 2010. Armonk (NY), USA: International Business Machines Corporation).

RESULTS

Fifty-one students, mean \pm SD age 14.5 years \pm 0.6; range: 13.6–15.7 years, 23 boys (45.1%) and 28 girls (54.9%) were enrolled in the study. Thirty-three students (64.7%, 15 boys, 18 girls) were assigned to the NAN group and 18 students (35.3%, 8 boys, 10 girls), who presented with at least one atypical naevus, were assigned to the AN group.

We found higher values for the AN group in all scales of ASS-SYM. These differences reached statistical significance in “nervousness and mental tension”, “psychophysiological dysregulation”, “burden of pain” and “general symptoms and problems”. Details are given in Table I.

Details concerning psychovegetative parameters are given in Table II.

In HR we found statistically significant differences between the two groups (AN vs. NAN) at R1 (74.6 [14.52] for NAN vs. 80.8 [8.38] for AN, $p=0.012$) and at R2 (76.2 [15.44] NAN vs. 81.3 [7.91] AN, $p=0.024$), but not during d2. Multivariate analysis of the repeated measures revealed a significant increase in HR from R1

Table I. Scales of the change-sensitive symptom list (ASS-SYM) in adolescents without (NAN) and with atypical naevi (AN)

ASS-SYM scale	NAN (n=33)	AN (n=18)
Physical and psychological exhaustion	8.0 (1.0–15.0)	10.0 (3.0–16.0)
Nervousness and mental tension	6.0 (0.0–17.0)*	9.0 (1.0–19.0)
Psychophysiological dysregulation	4.0 (0.0–17.0)*	5.5 (2.0–14.0)
Performance and behavioural problems	6.0 (0.0–18.0)	8.0 (2.0–19.0)
Burden of pain	4.0 (0.0–9.0)*	6.0 (0.0–12.0)
Self-determination and self-control problems	4.0 (0.0–20.0)	7.0 (1.0–14.0)
General symptoms and problems	32.0 (3.0–91.0)*	45.0 (14.0–83.0)

Values display median (range). *indicate statistically significant differences between NAN and AN.

to d2 in both groups (from 74.6 [14.52] to 86.9 [13.06] in NAN, $p<0.001$; from 80.8 [8.38] to 87.8 [12.22] in AN, $p<0.001$) and a significant decrease from d2 to R2 in both groups (down to 76.2 [15.44] in NAN, $p<0.001$; down to 81.3 [7.91] in AN, $p<0.001$). No group showed significant HR differences between R1 and R2.

In systolic blood pressure (sBP) we found no differences between the two groups at the 3 time points R1, d2 and R2. During the testing procedure sBP increased significantly from R1 to d2 in the AN (from 102.6 [13.68] to 117.1 [22.76], $p=0.012$) but not for the NAN group and decreased significantly from d2 to R2 in the NAN (from 110.0 [25.07] at d2 to 105.9 [12.01] at R2, $p=0.020$) but not in the AN group. No group showed significant sBP differences between R1 and R2.

In diastolic blood pressure (dBP) we found no differences between the two groups at the 3 time points R1, d2 and R2. In the course of the test procedure dBP increased significantly from R1 to d2 in both groups (NAN: from 66.6 [13.17] to 75.6 [16.58], $p=0.030$; AN: from 67.3 [10.60] to 75.5 [14.33], $p=0.004$) and a significant decrease from d2 to R2 in both groups (down to 65.0 [10.84] in NAN, $p<0.001$ and down to 65.9 [16.17] in AN group, $p<0.027$). No significant differences were found between R1 and R2 in both groups.

In BRS we found a significant difference between the two groups at R1 (NAN: 23.54 [10.14], AN: 16.01 [7.76], $p=0.008$) but not at d2 and R2. Within the NAN group we found significant differences among the time

Table II. Psychovegetative parameters in adolescents without (NAN) and with atypical naevi (AN) during the sequence of the test procedure

		First period of rest (R1)	Test of attention (d2)	Second period of rest (R2)	Sig.
Heart rate	NAN	74.55 (14.52)*	86.90 (13.06)	76.15 (15.44)*	a*** b***
	AN	80.80 (8.38)	87.78 (12.22)	81.32 (7.91)	a*** b***
Systolic blood pressure	NAN	107.6 (10.31)	110.0 (25.07)	105.9 (12.01)	b*
	AN	102.6 (13.68)	117.1 (22.76)	103.1 (15.27)	a*
Diastolic blood pressure	NAN	66.57 (13.17)	75.56 (16.58)	65.04 (10.84)	a* b***
	AN	67.32 (10.60)	75.49 (14.33)	65.90 (16.17)	a** b*
Baroreceptor sensitivity	NAN	23.54 (10.14)**	16.06 (7.97)	21.38 (13.49)	a*** b*
	AN	16.01 (7.76)	14.15 (6.79)	15.70 (12.52)	
Heart rate variability – ratio low frequency/high frequency	NAN	1.114 (0.864)*	1.519 (0.718)	1.171 (0.741)*	a* b*
	AN	1.695 (0.620)	1.860 (1.414)	1.654 (0.750)	

Asterisks attached to the values indicate statistically significant differences between NAN and AN; “Sig.” column showing statistically significant differences between R1 and d2 (a) and between d2 and R2 (b); statistical significance is classified as * $p<0.05$, ** $p<0.01$ and *** $p<0.001$; classification in column “Sig.” is based on *p*-values corrected for multiple comparisons.

points. In the NAN, BRS decreased from R1 (23.54 [10.14]) to d2 (16.06 [7.97], $p < 0.001$) and increased again up to 21.38 (13.49) ($p = 0.015$) in R2 with no significant difference between R1 and R2.

In ratio LF/HF we found significant group differences at R1 (NAN: 1.11 [0.86], AN 1.70 [0.62], $p = 0.020$) and at R2 (NAN: 1.17 [0.74], AN 1.65 [0.75], $p = 0.035$) but not at time d2.

During the testing procedure in the NAN group the LF/HF ratio increased from R1 (1.11 [0.86]) to d2 (1.52 [0.72], $p = 0.033$) and decreased again to 1.17 (0.74) ($p = 0.013$) at time R2 with no significant difference between R1 and R2. Within the AN group we found no significant differences at any time points.

DISCUSSION

Acute psychosocial/emotional stress is known to cause an increase in HR and the ratio LF/HF (34–36), and can lead to a reduction of HRV and baroreceptor control (16–19). Thus, the higher values in psychovegetative/psychocardiological parameters found in the periods of rest in adolescents with AN can be assumed to reflect a higher vegetative arousal. Conversely, the difference between LF/HF and other measured values in the two groups is not significant during mental stress: we can therefore assume mental stress to cause a comparable arousal both in adolescents with and without AN. Malignant melanoma is known as one of the most aggressive types of skin cancer and is also associated with a high mortality rate (37–39) as well as a steadily increasing incidence (40, 41).

More than 50 melanocytic naevi and/or the presence of atypical, so called dysplastic naevi, are associated with higher melanoma risk (42). Recent investigations have shown a 10 times higher risk in individuals with so called dysplastic or AN (43). UV radiation is likely to play a major role in the pathogenesis of atypical naevi (44) but also other pathogenetic factors have been ascertained for this type of naevi, such as genetic disposition, hormonal changes, e.g. elevated levels of growth hormones and immunosuppression (2).

Naevogenesis of AN is unclear. They are acquired naevi caused by genetic disposition with a distinct clinical appearance differentiating from classical acquired reticular naevi (1, 2). As the appearance of the first atypical naevus is observed more often around puberty, the onset of these naevi might be influenced by hormonal changes, but other factors should also be considered. In our study, students with at least one AN showed signs of higher psychological and physiological strain leading to the speculation that strain could be a co-founding factor responsible for the presence of this type of naevi.

Not only for sun exposure, but also for physical strain an association with an increased number of naevi has been observed (11). Also, chronic stress as well as maladaptive stress-coping-strategies appear to be as-

sociated with immunosuppression (45, 46), which, in turn, in the presence of AN may lead to increased rates of malignant melanoma (2, 47–51).

The size of the sample and the provenance of the participants from only one secondary school greatly limit the generalisability of our results. Thus, the results of this exploratory study must be verified on a larger sample, also considering different age groups. General symptoms and problems were asked in order to estimate the psycho-emotional strain of the students. More specific information on the possible relationship of AN and stress should also be obtained in further studies by considering different aspects of resilience. Taking into consideration that the participants did not know their number of AN we can suppose that the higher level of strain, both on a psychological and vegetative level, was not influenced by the fear of the forthcoming skin examination, because the skin examination was performed after the test procedure.

In conclusion, our data provide one more element linking "mental" and "physical" features by showing that AN are associated both with a higher physiological and psychological strain (40, 52–54).

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