

Effects of oral isotretinoin treatment for acne vulgaris patients on anger responses and the relationship with temperament

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SUMMARY

OBJECTIVE: Isotretinoin is the only medication against all the factors involved in acne vulgaris pathogenesis. The aim of our study was to verify whether patients with acne vulgaris receiving isotretinoin therapy exhibit elevated anger levels and to observe the correlation between age, temperament traits, and anger.

METHODS: The study group comprised a sum of 100 cases, involving 50 individuals with acne vulgaris-required high-dose retinol therapy and 50 controls who did not start any medication.

RESULTS: Our study showed that anger levels increased with drug use. A positive correlation between cyclothymic temperament, the anxiety-related behavior subdimension, and the introvert and passive-aggressive subdimension of interpersonal anger reactions has been recognized. In addition, a positive one was observed between hyperthymic temperament and the introvert subdimension, which is one of the anger-related thoughts and interpersonal anger reactions.

CONCLUSION: This study elucidates anger dimensions such as anger-related thoughts, behaviors, and reactions in individuals who received retinol treatment for acne vulgaris. In addition to anger and its dimensions, temperament was also investigated. Although several studies have investigated the relationship between acne vulgaris and psychiatric symptoms, to the best of our knowledge, no research has been reported in the English-language literature regarding the relationship between anger dimensions and temperament after retinol treatment that might make our study an original and valuable contribution to the literature.

KEYWORDS: Acne vulgaris. Anger. Isotretinoin. Aggression. Side effects. Temperament.

INTRODUCTION

Acne vulgaris (AV), *per se*, is a disease characterized by inflammatory changes in the pilosebaceous follicles occurring in the form of comedones, papules, pustules, nodules, and cysts that may cause appearance disorders due to serious permanent scarring. Generally, the disease is defined to affect adolescents and young adults with different clinical appearances, and the severity of the disease and the individual's perceptions may be different¹. There are at least three types of interaction proposed between AV and mental factors: (1) there is a complicated relationship between stress and AV involving the neuroimmune cutaneous system and hypothalamic-pituitary axis with AV observed or becoming more severe via this pathway; (2) AV develops secondarily in patients with psychiatric symptoms such as anxiety, depression, social phobia, and low self-esteem; and (3) just as in body dysmorphic disorder, a primary psychiatric disorder is the focus of acne². *De facto*, isotretinoin is the only medication affecting all factors playing a role in the pathogenesis of acne³, and its correlation with depression, anxiety, and anger control is still a controversial

issue. The high incidence of depression in society makes it difficult to distinguish depression triggered by other causes like isotretinoin. When the literature studying depression as a side effect of isotretinoin is examined, in general, there is no common point with studies proposing that isotretinoin causes depression mainly in the form of case reports and limited controlled studies supporting the correlation between isotretinoin and depression. Contrarily, many retrospective and prospective controlled studies conclude no significant correlation between isotretinoin and depression. However, cases developing depressive symptoms during isotretinoin therapy exhibit that patients need to be closely monitored for the development of anxiety and depression during the treatment process⁴. Some authors state that acne should be dealt with as an organic event with personality traits having no effect on the development of acne⁵, while some identify the disrupted quality of life⁶, high anger levels⁷, and difficulty in terms of social and functioning¹ among acne cases.

This study purposed first to test whether there is an increase in anger levels at the scale level observed in clinical practice

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among AV cases treated with isotretinoin and second to observe the correlation between temperament traits and anger. In this way, we aimed to draw more attention to the psychological effects of isotretinoin, which is frequently used in AV by dermatologists in clinical practice, and to raise awareness about the initiation of treatment in patients at risk in cooperation with psychiatrists.

METHODS

Ethical aspects

This study was conducted according to the Declaration of Helsinki and approved by the Clinical Research and Ethics Committee linked to Ordu University (No. #2014/01).

Study design

This study incorporated a sum of 100 cases, including a 50-person patient group admitted to the Dermatology Clinic due to AV and started high-dose isotretinoin and a 50-person control who had not possessed isotretinoin but only antibiotics and local acne medication between January 2017 and March 2018. The study examined the correlation between age, multidimensional anger levels, and temperament traits of patients attending our clinic due to AV grades 4–5 according to the Global Acne Severity Scale and beginning high-dose isotretinoin. In addition, whether there was a difference in multidimensional anger levels based on sex and educational status of participants had been investigated, along with the variations in multidimensional anger levels in the patient group in three different periods (i.e., initial, first month, and third month). Our exclusion criterion was that the patients had previously or currently received psychiatric treatment. This assessment was made on the basis of the patients' statements. As such, three diagnostic tools were used to collect the necessary information: (i) the Sociodemographic and Clinical Information Form, (ii) the Multidimensional Anger Scale (MAS), and (iii) the Temperament Scale (TEMPS-A). To this end, informed consent had been given to all patients, and their signatures were obtained.

Data collection tools

In this research, three tools were used to collect the necessary information:

1. Sociodemographic and Clinical Information Form
2. MAS
3. TEMPS A temperament scale

Sociodemographic and Clinical Information Form:

In accordance with the aim of the research, this tool was developed by the researchers to collect information about socio-demographic and clinical data.

MAS:

The scale was developed by Balkaya and Şahin⁸ with the aim of determining feelings, thoughts, and attitudes about anger in individuals, and validity and reliability studies were completed. The MAS comprises 158 items inquiring about five different dimensions⁸.

Temps-A Temperament Scale:

Being developed by Akiskal, this scale comprises 100 items to determine 5 temperaments⁹, namely, depressive, cyclothymic, hyperthymic, irritable, and anxious. Individuals answer the questions with yes or no based on consideration of all experiences. The Turkish validity and reliability study was completed by Vahip et al¹⁰.

Statistical analyses

The Cronbach's alpha internal consistency coefficient was calculated for reliability studies for answers given by patients with AV to the MAS. According to the Shapiro-Wilk test (for $n < 50$) results, the points for the MAS as a whole and for each subdimension used in the research had a normal distribution in terms of error ($p > 0.05$). *In fine*, differences between total points for scales and subdimensions in terms of the patient group and sex were determined with the Student's t-test, whereas differences in terms of educational status were determined with the one-way analysis of variance and the Tukey's multiple comparison test. Additionally, the correlation between patient age, multidimensional anger levels, and temperament traits was examined with the Pearson correlation coefficient.

RESULTS

The participants in the study were divided into two groups in the initial period based on whether or not they were taking retinoic acid. In terms of responses to the MAS, the points obtained for the thoughts related to the anger dimension (not taking retinoic acid=70.04; taking retinoic acid=79.74) were identified to be significantly different. Responses of participants to the anger scale for isotretinoin and control groups are summarized in Table 1. In the initial period, there were no significant differences identified in terms of responses to the MAS based on the gender and educational status of participants ($p > 0.05$).

In terms of responses to the MAS in the third month, the patients taking retinoic acid had statistically significantly higher points for the dimension of thoughts related to anger and all

Table 1. Participant responses to multidimensional anger scale in the beginning and third month.

Beginning-Multidimensional Anger Scale	Isotretinoin (n=50)	Control (n=50)	p-value
Thoughts related to anger	79.74±17.68	70.04±12.04	0.002*
Anger-oriented thought	19.26±9.25	18.62±5.94	0.691
Angry thoughts toward others	20.66±7.81	19.82±6.22	0.553
Angry thoughts toward themselves	15.68±5.70	15.26±4.37	0.680
Angry thoughts toward the world	10.70±5.40	10.90±4.74	0.844
Behavior related to anger	69.16±14.76	70.04±12.04	0.745
Aggressive	27.20±8.66	25.60±8.03	0.340
Calm	29.78±8.60	31.50±6.77	0.269
Anxious	12.18±3.22	12.94±2.88	0.217
Interpersonal anger reactions	122.80±37.20	132.68±33.06	0.164
Revenge	55.28±22.11	58.58±20.95	0.445
Passive-Aggressive	31.64±9.18	33.18±8.40	0.542
Introversion	29.70±8.47	31.84±6.95	0.170
Unconcerned	8.18±3.21	9.08±3.57	0.188
Third month Multidimensional Anger Scale	Isotretinoin (n=50)	Control (n=50)	p-value
Thoughts related to anger	79.06±26.70	70.04±12.04	0.002*
Anger-oriented thought	24.04±8.72	18.62±5.94	0.001*
Angry thoughts toward others	23.78±8.22	19.82±6.22	0.008*
Angry thoughts toward themselves	18.36±6.14	15.26±4.37	0.004*
Angry thoughts toward the world	12.88±5.02	10.90±4.74	0.045*
Behavior related to anger	79.74±17.68	70.04±12.04	0.002*
Aggressive	35.40±9.39	25.60±8.03	0.001*
Calm	31.02±9.39	31.50±6.77	0.738
Anxious	13.32±3.11	12.94±2.88	0.528
Interpersonal anger	145.56±35.29	132.68±33.06	0.063

*p<0.005.

subdimensions (thoughts about anger, angry thoughts toward others, angry thoughts toward themselves, and anger thoughts toward the world), points for the revenge subdimension of the interpersonal anger reaction dimension, the behavior related to anger dimension, and the aggressive subdimension compared with patients not taking retinoic acid. The differences between responses to the MAS based on the gender of participants in the third month are given in Table 1. In terms of responses to the MAS in the third month, there were no statistically significant differences identified between male and female participants and on educational status in terms of all dimensions and subdimensions.

The variation over time of responses to the MAS initially and in the first and third months of patients taking retinoic acid is given in Table 3. There was a linear increase in points determined over time for all dimensions and subdimensions

(apart from passive-aggressive and introversion) for responses of patients receiving retinoic acid to the MAS from initially to the first and the third months ($p<0.05$) (Table 2).

The correlation levels and significance between patients' age, multidimensional anger levels, and temperament traits are given in Table 3. According to correlation analysis, the thoughts about the anger subdimension of the MAS were positively and significantly correlated with depressive temperament, and hyperthymic temperament on the TEMPS scale. There were positive and significant correlations identified between depressive temperament and thoughts about anger, angry thoughts toward others, angry thoughts toward themselves, and angry thoughts toward the world. There were positive significant correlations between depressive temperament and the interpersonal anger reaction subdimension of anxious reaction, and the behavior related to the anger subdimension of introverted behavior. There were

Table 2. Comparison of patients responses to the multidimensional anger scale in the beginning and in the third month.

Multidimensional Anger Scale	Initial (n=50)	Third month (n=50)	p-value
Thoughts related to anger	79.74±17.68	79.06±26.70	0.001*
Anger-oriented thought	19.26±9.25	24.04±8.72	0.001*
Angry thoughts toward others	20.66±7.81	23.78±8.22	0.001*
Angry thoughts toward themselves	15.68±5.70	18.36±6.14	0.001*
Angry thoughts toward the world	10.70±5.40	12.88±5.02	0.001*
Behavior related to anger	69.16±14.76	79.74±17.68	0.001*
Aggressive	27.20±8.66	35.40±9.39	0.001*
Calm	29.78±8.60	31.02±7.49	0.009*
Anxious	12.18±3.22	12.26±3.32	0.014*
Interpersonal anger reactions	122.80±37.20	145.56±35.29	0.001*
Revenge	55.28±22.11	72.68±20.04	0.001*
Passive-Aggressive	29.64±9.15	31.72±8.71	0.084
Introversion	29.70±8.47	31.18±7.71	0.078
Unconcerned	8.18±3.21	9.98±2.23	0.001*

*p<0.005.

positive and significant correlations identified between cyclothymic temperament with anxious response, passive-aggressive, and introversion subdimensions. There were positive and significant correlations between hyperthymic temperament and angry thoughts toward others, angry thoughts toward themselves, angry thoughts toward the world, interpersonal anger reactions, and introverted behavior related to anger. For irritable temperament, there were positive significant correlations with revenge, related to anger, passive-aggressive, and introverted behavior subscales, and a negative significant correlation with the aggressive subscale of the interpersonal anger reactions. For anxious temperament, there was a positive significant correlation found with the revenge behavior related to the anger subscale.

DISCUSSION

Acne dermal lesions, *per se*, are a chronic inflammatory disease of the skin of *Homo sapiens* which might lead to low self-esteem, anxiety, depression, and stigmatism which might frequently impair the quality of life seriously¹¹⁻¹³. Mental effects may give rise to AV which might increase the risk of anxiety, depression, and suicide¹⁴. Moreover, retinoic acid is a drug that is recommended for treating nodulocystic acne but is used in milder forms and affects more than one mechanism^{15,16}. Anger has been revealed as a variable in many studies; however, as far as we are aware, no study that examines the subdimensions of anger, such as thoughts, behaviors, and reactions, that may develop in stages in patients with retinol therapy

has been conducted. When patients with and without retinol administration were examined in the analyses performed, the anger-related thoughts (anger-related thoughts toward others, one's self, and the world) increased significantly in the measurements performed at the end of the third month compared with the first month. In the measurement performed during the first application, there was a significant increase in the anger-related thought dimension and in all subdimensions in the third month. While the anger response was in the form of passive-aggressive in the first month, it was in the form of revenge in the measurements in the third month. While the patients did not define any behaviors related to anger at the beginning, they stated that they presented their anger as aggression in the third month. Our study showed that anger levels increased with drug use. In another study that supported the results of our study, it was revealed that the irritability of the patients significantly increased at the end of the third month with the use of medication¹⁵. Moreover, meta-analysis studies showed a significant relationship between retinoic acid use and mood disorders^{17,18}. However, there are studies that do not support that drug use causes an increase in psychiatric diseases¹⁹. Averil et al. demonstrated that men and women were similar in terms of anger styles²⁰, which is consistent with our study. However, some studies concluded that anger revealed a significant difference between men and women, that anger and aggressive behaviors were more common in men than women, and that men directly expressed their feelings of anger. Although some studies show that anger responses decrease with

Table 3. Correlations between multidimensional anger levels and temperament characteristics.

Dimension and subdimensions	DepressiveT	CycloT	HyperthymicT	IrrT	AnxiousT
Thoughts related to anger					
r-value	0.307	0.147	0.220	-0.022	0.111
P-value	0.002	0.146	0.028	0.829	0.271
Anger-oriented thought					
r-value	0.254	0.145	0.189	-0.073	0.098
P-value	0.011	0.150	0.060	0.473	0.330
Angry thoughts toward others					
r-value	0.283	0.108	0.201	-0.005	0.116
P-value	0.004	0.286	0.045	0.960	0.251
Angry thoughts toward themselves					
r-value	0.254	0.070	0.204	-0.062	0.068
P-value	0.011	0.491	0.041	0.542	0.500
Angry thoughts toward the world					
r-value	0.348	0.228	0.221	0.087	0.122
P-value	0.000	0.022	0.027	0.389	0.226
Interpersonal anger reaction					
r-value	0.120	0.024	0.250	-0.109	0.036
P-value	0.234	0.816	0.012	0.278	0.723
Aggressive					
r-value	0.017	-0.037	0.284	-0.260	-0.024
P-value	0.869	0.713	0.004	0.009	0.815
Calm					
r-value	0.147	0.010	0.102	0.078	0.075
P-value	0.145	0.921	0.311	0.439	0.459
Anxious					
r-value	0.231	0.226	0.132	0.102	0.091
P-value	0.021	0.024	0.191	0.312	0.370
Behavior related to anger					
r-value	0.179	0.276	0.252	0.106	0.035
P-value	0.074	0.005	0.012	0.295	0.731
Revenge					
r-value	0.174	0.150	0.190	0.440	0.205
P-value	0.076	0.129	0.058	<0.001	0.042
Passive-Aggressive					
r-value	0.116	0.348	0.158	0.235	0.165
P-value	0.250	<0.001	0.116	0.018	0.102
Introversion					
r-value	0.284	0.317	0.209	0.270	0.086
P-value	0.004	0.001	0.037	0.007	0.395
Unconcerned					
r-value	0.134	-0.034	0.146	0.005	0.004
P-value	0.185	0.735	0.146	0.964	0.972

r are the correlation coefficients between examined traits; P-value are significant values.

age, some report that there is no difference in terms of anger symptoms. This study did not reveal a significant correlation between age and dimensions of anger. The results of our study support the positive correlation between depressive temperament and all subdimensions of anger-related thoughts, the anxiety behavior subdimension of anger-related thoughts, and the introvert subdimension of interpersonal reactions. Our study supports the positive correlation between cyclothymic temperament and the anxiety-related behavior subdimension, and the introvert and passive-aggressive subdimension of interpersonal anger reactions. Individuals with hyperthymic temperament, however, draw a profile that is friendly, extroverted, overly talkative, self-confident, optimistic, and well-planned. When the relationship between hyperthymic temperament and anger is examined, our study supports the positive correlation between hyperthymic temperament and the introvert subdimension, which is one of the anger-related thoughts and interpersonal anger reactions. This result can be thought of as a reaction that is inconsistent with the hyperthymic temperament trait. However, due to their overly optimistic nature, they may be using the rationalization defense mechanism a lot and may not have an open reaction which can be considered a reaction that is inconsistent with the hyperthymic temperament trait^{8,17,21}. Our study supports the positive correlation between irritable temperament and revenge, passive-aggressive, and introvert subdimensions of interpersonal anger responses. However, irritable temperament, which is negatively associated with the offensive subdimension of anger-related behaviors, does not reflect the expected result; the low sample size may have caused this result. We stated a positive correlation between the revenge subdimension for interpersonal anger reactions and anxious temperament. However, although it was expected that the results of the research would be significant in the anxious subdimension, this result was not obtained; this result possibly changes as the number of samples and the number of patients with an anxious temperament increase.

Limitations

The first limitation of our study was the small sample size, as mentioned above. Furthermore, the heterogeneity level was not sufficient because the study was conducted only in Ordu

City. Therefore, the results may have affected the generalization of the population because of both the insufficient number of samples and the homogeneity of the sample. Another limitation was that multiple scales were simultaneously used. According to the observations made, patients may have been bored and had difficulty filling in the scales. As these were self-report scales, the answers received were evaluated on the assumption of sincerity.

CONCLUSION

This study elucidates anger dimensions such as anger-related thoughts, behaviors, and reactions in individuals who received retinol treatment for AV. In addition to anger and its dimensions, temperament was also investigated. Despite all limitations, this study attempted not only to obtain general data about anger but also to elucidate anger dimensions such as anger-related thoughts, behaviors, and reactions in individuals who received retinol treatment used in AV disease. Although several studies have investigated the relationship between AV and psychiatric symptoms, no research has been reported regarding the relationship between anger dimensions and temperament after retinol treatment which might give our study an original and valuable contribution to the literature. Well diagnosed, well cared for. Considering that there are few studies on this subject in the literature, it is obvious that more studies on the psychiatric effects of isotretinoin, which is highly effective in the treatment of severe and persistent AV, are needed.

ETHICAL APPROVAL

This study was approved by the Ordu University, Ordu, Turkey (approval no: #2014/01).

AUTHORS' CONTRIBUTIONS

EYD: Conceptualization, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **ÖKK:** Data curation, Visualization.

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