Original Research

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Effect of Hypnotherapy on Immune Response and Standard Therapy in Psychogenic Asthma Patients

Psikojen Astım Hastalarında İmmün Cevap ve Standart Tedavi Üzerinde Hipnoterapinin Etkisi

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Abstract

Objective: Asthma is a complex inflammatory disease. The therapy for asthma is usually pharmacotherapy but it can increase the side effects in the long run. Hypnosis has been used to clinically treat asthma. This study aimed to investigate the efficacy of hypnotherapy which will increase the standard of therapy in psychogenic asthma patients on immune response, stress mediators, and asthma control level.

Materials and Methods: This research is a double-blind experimental randomized control trial group study with a crossover design conducted in the outpatient clinic of Dr. Moewardi Hospital, Surakarta, Indonesia. The Friedman test followed by the marginal homogeneity statistic test was used to assess variations in the levels of asthma control. The study subjects were 30 respondents who were divided randomly into groups A and B. Both groups had standard asthma therapy and hypnotherapy with a different sequence.

Results: Hypnotherapy made a significant decrease in SCL 90 score within each group as follows: Group A (A1 vs A2; p=0.004) and Group B (B2 vs B3; p=0.001). Levels of asthma control improved significantly in both groups (A1 vs A2; p=0.001) and B2 vs B3; p=0.004). Hypnotherapy significantly improved the norepinephrine levels in both groups as well (A1 vs A2; p=0.001) and B2 vs B3; p=0.003). Hypnotherapy insignificantly reduced IL-13 (p=0.132) and IL-17 (p=0.149) levels.

Conclusion: This study concluded that hypnotherapy applied to psychogenic asthma patients can improve their standard therapy response. This improved standard therapy response will affect the treatment, prevention, and management of uncontrolled asthma.

Keywords: Asthma control level, cortisol, hypnotherapy, IL-13, IL-17, norepinephrine, psychogenic asthma

Öz

Amaç: Astım, kompleks inflamatuvar bir hastalıktır. Astım tedavisi genellikle farmakoterapidir ancak uzun vadede yan etkileri arttırabilir. Hipnoz, astımın klinik olarak tedavi edilmesi için kullanılmaktadır. Bu çalışmanın amacı, immün cevap, stres mediatörleri ve astım kontrol seviyesine ilişkin olarak psikojen astım hastalarında tedavi standardını arttıracak olan hipnoterapinin etkililiğini araştırmaktır.

Gereç ve Yöntem: Bu araştırma, Surakarta, Endonezya'da bulunan Dr. Moewardi Hastanesinin polikliniğinde yürütülen çapraz tasarımlı bir çift kör, deneysel, randomize kontrollü bir deney grubu çalışmasıdır. Astım kontrolü seviyelerindeki varyasyonları değerlendirmek için Friedman testi ve ardından marjinal homojenlik testi kullanıldı. Çalışmada rastgele yöntem ile A ve B gruplarına ayrılmış 30 hasta yer aldı. Her iki grup da, farklı bir sırayla standart astım tedavisi ve hiponoterapi aldı.

Bulgular: Hipnoterapi, aşağıda belirtilen şekilde her grup içinde SCO 90 skorlarında anlamlı bir azalma sağladı: Grup A (A1 vs A2; p=0.004) ve Grup B (B2 vs B3; p=0.001). Astım kontrol seviyeleri, her iki grupta da anlamlı olarak iyileşme gösterdi (A1 karşı A2; p=0.001 ve B2 karşı B3; p=0.004). Hipnoterapi, yine her iki grupta, norepinefrin seviyelerini anlamlı olarak iyileştirdi (A1 karşı A2; p=0.001 ve B2 karşı B3; p=0.073). Hipnoterapi, IL-13 (p=0.132) ve IL-17 (p=0.149) seviyelerini istatistiksel olarak anlamlı olmayan düzeylerde azaltı.

Sonuç: Bu çalışma, psikojen astım hastalarına uygulanan hipnoterapinin standart tedaviye verdikleri yanıtı iyileştirebildiği sonucuna varmıştır. Bu gelişmiş standart tedavi yanıtı da kontrolsüz astımın tedavisini, önlenmesini ve tedavisini etkileyecektir.

Anahtar kelimeler: Astım kontrol seviyesi, kortizol, hipnoterapi, IL-13, IL-17, norepinefrin, psikojen astım

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Introduction

Asthma is a complex inflammatory disease characterized by airway inflammation and hyperresponsiveness.^[1] It is one of the most common non-communicable chronic diseases affecting around 334 million people worldwide.^[2] The prevalence of asthma increases both domestically and globally. The highest prevalence is seen in the developed and the lowest in the developing countries,^[3] such as Indonesia. The high frequency of visits to emergency units due to exacerbation of asthma demonstrates the failure of prevention-oriented treatment, as mostly exacerbation of asthma can be prevented by good management.4 Meanwhile, the prevalence of asthma in Indonesia is 2.4% with a recurrent rate of 57.5% based on reported health statistics.^[5]

Inadequate control of asthma is strongly related to the presence of depressed mood in adults in the general population. [6] A study from China indicated that work and family stress are strongly related to asthma in Chinese women. [7] The long-term and recurrent exposure to psychological stress in asthma activates the axis of the hypothalamuspituitary-adrenal (HPA) axis and sympathetic adrenomedullary (SAM) system, inducing the secretions of cortisol, adrenaline (epinephrine), and nora- drenaline (norepinephrine), which can decrease the immune-protection function and increase TH2 response. [8,9] Stress can modify the activities of the HPA axis and SAM. Sympathetic-adrenalmedullary system comprises of sympathetic and parasympathetic branches that have effector molecules like epinephrine, norepinephrine, and acetylcholine. Lymphocytes and monocytes express the receptors for several stress hormones, including corti- cotropin-releasing hormone, adrenocorticotropic hor- mone (ACTH), cortisol, epinephrine, and norepinephrine.[10] Thus, the neuroendocrine hormones released during stressful conditions (epinephrine and norepinephrine) can alter the immune function and the course of the disease based on immunity.[11]

Asthma therapy is only depending on pharmacotherapy, but long-time pharmacotherapy increases the side effects and psychological stress factors, which are predisposing factors for worsening the condition of asthma patients. [12] Hypnosis has been used clinically for various disorders that are resistant to drug therapy, including asthma. However, the use of clinical hypnotherapy as stan dard therapy for asthma is still unknown. A study by Brown described that hypnosis had been effective on both the management of emotional stress, the cause of exacerbation of airway obstruction, and the stabilization of airway hyperresponsiveness among asthma patients. [13] A study by Freeman and Welton also stated that asthma

patients' conditions had improved after imagery-hypnosis, although this treatment has not been recommended as stan dard therapy for asthma. [14] We aimed to investigate the effect of hypnotherapy on immune response, stress mediators and degree of psychogenic asthma.

Material and Methods Research design

This double-blind experimental randomized controltrial group study with crossover design was performed on asthma patients visiting the outpatient pulmonary clinic of Dr. Moewardi Hospital, Surakarta, Indonesia, between September 2014 and May 2015. This study was reviewed by the Health Research Ethics Commission of Dr. Moewardi Hospital (registration number 405/V/ HREC/2015). Based on the sample size formula for unpaired numerical analytic research, the minimum sam- ple size for each group was 10 patients. Thirty patients were randomly divided into Groups A and B. We initially evaluated the clinical assessment, levels of asthma control, norepinephrine, and cortisol for both groups. Group Awas given standard therapy and six sessions of hypnotherapy for 6 weeks, continued with a reevaluation of asthma con- trol level. For Group B, 6 weeks after the first evaluation, we reevaluated the asthma control level and continued to give standard therapy and six sessions of hypnotherapy for another 6 weeks and then evaluated the asthma control level once again. The crossover study design is shown below.

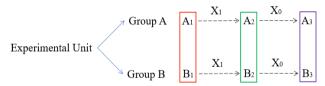


Figure 1. Crossover study design.

Note:

O=Observation (Clinical measurement, norepineph- rine, and cortisol levels) were done on O_1 (red), O_2 (green), and O_3 (purple).

 X_n =Without hypnotherapy; X_1 =Hypnotherapy for 6 times;

 A_1 =Group A before hypnotherapy; A_2 =Group A after hypnotherapy; A_3 =Group A without hypnotherapy

 B_1 =Group B without hypnotherapy; B_2 =Group B before hypnotherapy; B_3 =Group B after hypnotherapy

The patients with the following characteristics and met the required criteria were included in our study: controlled or uncontrolled asthma based on Global Initiative for Asthma (GINA) 2012 criteria, psychogenic (asthma triggered by psychological stress factors) and nonatopic (neutrophilic) asthma, 18-45 years old, at least graduated from junior high school, able to speak Bahasa Indonesia, nonsmoker, did not meet asthma-COPD overlap syndrome (ACOS) criteria, and willing to participate in our study by signing informed consent. The patients with severe psychiatric disorder determined by an interview assessment

method, severe physical dysfunction, and hearing problem hindering verbal communication were excluded from our study. Thirty-seven patients met our inclusion criteria, but 7 of them dropped out, leaving 30 patients to be randomly assigned into Groups A and B as previously mentioned.^[7]

Hypnotherapy procedure

The hypnotherapy was applied with induction, followed by several sequences of suggestions to alter the general obser- vation in subjective experience, such as the alterations of sensation, perception, emotion, thought, or behavior. The short-term hypnotherapy was performed six times with sen- sory-imagery conditioned technique. The Peak expiratory flow (PEF) was measured with a peak flow meter (PF).

Asthma was clinically described as controlled, partially controlled, and uncontrolled based on GINA 2012 criteria, ^[10] using the most current clinical control (for 4 weeks) based on the following criteria and characteristics:

1) Daytime symptoms: Controlled ($\leq 2x / \text{week}$), and partially controlled (> 2x/week); 2) Activity limitation: partially controlled; 3) Waking up at night: partial controlled, and uncontrolled (3 or more times partially controlled in a week); 4) Need for reliever: controlled ($\leq 2x$ / week), and partially controlled (> 2x/week); 5) Lung function Forced expiratory Volume1 (FEV1)/ Force vital capacity (FVC): controlled (normal), and partially controlled (< 80% pre- dicted or the one if any). The applied hypnosis to control asthma used three targets; 1) Anxiety component: patients were guided to enter a hypnotic state and use their imaginations to produce holistic relaxation; 2) Conditioned response to a component that triggered asthma recurrence: patients were in a hypnotic state and joyful suggestions were used to create a comfortable response for specific environment component; 3) Physiological response to a substance that triggered asthma recurrence: patients were guided to enter a hypnotic state and to focus on the sugges tion to alter their breathing activity. This was useful to reframe the substance that triggered asthma as a common substance for those individuals.[9]

Table 1. Demographic characteristics of the patients.

IL-17 were measured from 5 ml of blood serum samples. They were centrifuged and analyzed using the ELISA method. The blood serum samples were taken at the same time before and after hypnotherapy.

The levels of norepinephrine, cortisol, IL-13, and

Statistical analysis

The descriptive data were presented in mean±SD or median and the frequency was presented in percentages. The variation or mean difference of asthma control level for paired data with >2 categories (uncontrolled, partially controlled, and totally controlled) and total repetition of >2 (before treatment, pre-, and post crossover) was analyzed statistically using the Friedman test followed by the marginal homogeneity test. A Cochrane test followed by the McNemar test was used for a paired categorical comparative test of asthma control characteristics. It was considered statistically significant if the p-value was <0.05.

Results

Demographically, there were no significant different characteristics between the two groups regarding BMI (p=0.330), Symptom Checklist-90 (SCL-90) score (p=0.693), female sex (p=0.690), and asthma family history (p=0.142). Age was significantly different, as we found older patients in Group A (p=0.004) and educational level was higher in Group B than Group A (p=0.001) (Table 1).

The baseline characteristic of patients regarding asthma control level based on GINA criteria showed no significant difference between the two groups (p >0.05). There were eight uncontrolled asthma patients in both groups (Group A vs Group B; p=1.000). The criteria for evaluating asthma control level included the daily asthma symptoms (Group A vs group B; p=0.624), waking up at night (Group A vs Group B; p=0.456), the use of reliever (Group A vs Group B; p=1.000), limitation of activity (Group A vs Group B; p=1.000), and VEP1 lung function (Group A vs Group B; p=0.833) (Table 2).

	mean		
Characteristics	Group A (n=15)	Group B (n=15)	p value
Age (th)	56.2±14.4	40.1±13.7	0.004*
BMI (kg/m ²)	24.60±5.50	23.00±3.19	0.330*
SCL-90 score	90.33±38.14	85.47±27.91	0.693*
	n (%)	n (%)	
Female	11/15 (73.3)	10/15 (66.7)	0.690**
Smoking	6/15 (40.0)	2/15 (13.3)	0.099**
Family history of asthma	14/15 (93.3)	11/15 (73.3)	0.142**
Higher Education Level	3/15 (20.0)	12/15 (80.0)	0.001**

^{*}Independent-samples T-test; **Chi-square test

Table 2. Criteria of valuating levels of asthma control.

	Group A (n= 15)		Group B (n=15)		
Levels of asthma control	n	%	n	%	p value
Uncontrolled	8	53.3	8	53.3	1.000**
a) Daytime symptoms > twice/week	13	86.7	12	80.0	0.624**
o) Nocturnal symptoms / awakening	10	66.7	8	53.3	0.456**
e) Need for reliever/ rescue treatment > twice/week	10	66.7	10	66.7	1.000**
l) Limitations of activities	5	33.3	5	33.3	1.000**
Lung function (FEV1)	mean	SD	mean	SD	
	71,35	18.08	72.25	14.93	0.883*

^{*}Independent-samples T-test; **Chi-square test

The effect of hypnotherapy on SCL-90 scores

SCL-90 scores were compared before and after hypnotherapy using the Wilcoxon test, and a significant decrease in SCL-90 scores was found [Group A, 90.3±38.1 vs 69.9±13.9 (p=0.004); Group B, 85.5±27.9 vs 63.6±17.4 (p=0.001)]. This analysis demonstrated that the hypnotherapy for psychogenic asthma patients who received standard therapy could lower the SCL-90 scores (Figure 2).

The effect of hypnotherapy on the improvement of the asthma control level

Our analysis showed that hypnotherapy improved asthma control significantly in both groups (p<0.001). Daily asthma symptoms, waking up at night, the use of reliever, and VEP1 lung function. Shows improvement after the hypnotherapy session, both in group A or B (Table 3). Our analysis revealed that hypnotherapy significantly improved asthma control level, from the levels of uncontrolled, partly controlled, to controlled asthma.

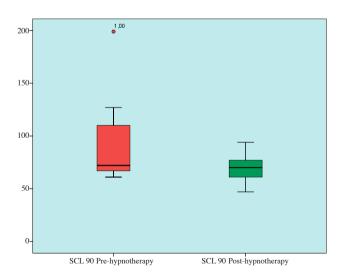


Figure 2. The effectiveness of hypnotherapy to SCL-90.

Modulation of stress mediators with hypnotherapy

This study indicated that hypnotherapy could increase the norepinephrine levels in both Groups A, and B (Figure 3). In Group A, the norepinephrine level increased from 52.7 ng/mL to 321.1 ng/mL (p=0.001) before and after hypnotherapy, respectively. Meanwhile, in Group B, the norepinephrine level increased from 214.29 ng/mL to 276.89 ng/mL (p=0.073) after hypnotherapy.

Hypnotherapy could decrease serum cortisol levels in psychogenic asthma patients, but this reduction was not significant in both Groups A and B (Figure 4). In Group A, serum cortisol level decreased from 10.38 ng/mL to 9.8 ng/mL (p=0.820) after hypnotherapy, while the serum cortisol level decreased from 11.37 ng/mL to 9.48 ng/mL (p=0.110) after hypnotherapy in Group B.

Hypnotherapy modulation in the immune mediator

Hypnotherapy in both groups, though not significantly, could reduce serum IL-13 levels (p=0.132) (Table 4). The IL-13 levels were lower after hypnotherapy (group A2)

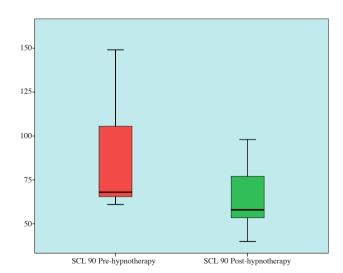


Table 3. The comparison of asthma control variables before and after hypnotherapy.

	Group A	A (n= 15)		Group B (n= 15)		
Levels of asthma control	Pre- hypnotherapy	Post- hypnotherapy	p value	Pre- hypnotherapy	Post- hypnotherapy	p value
Daytime symptoms >twice/week	86.7	0.0	<0.001**	73.3	33.3	0.014**
Nocturnal symptoms / awakening	66.7	0.0	0.002**	46.7	26.7	0.180**
Need for reliever / rescue treatment >twice/week	66.7	0.0	0.002**	73.3	40.0	0.025**
Limitations of activities	33.3	0.0	0.025**	20.0	6.7	0.157**
Lung function (%FEV1)	71.35	74.9	0.024*	74.6	77.0	0.011*

^{*}Paired T-test, **Wilcoxon test

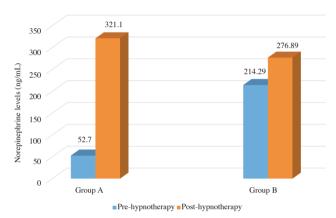


Figure 3. Effects of hypnotherapy on serum norepinephrine levels.

than without hypnotherapy (group A3). Without and after hypnotherapy the IL-13 level was 4.58 pg/mL and 1.65 pg/mL respectively.

Hypnotherapy in both groups, albeit not significantly, could reduce IL-17 levels as well (p=0.149) (Table 5). Mean Il-17 levels were 0.28 pg/mL and 0.33 pg/mL without and after hypnotherapy respectively.

Psychogenic asthma is precipitated by psychological stress factors.[15] Psychological problems may affect the change of health behavior such as alteration of self-efficacy to control asthma as well as the increase of anxiety or fear of asthma symptoms. [16] This will result in poor asthma management due to decreased adherence to medications, PF monitoring, and smoking cessation recommendations; delayed treatment, failure to avoid irritants or allergens from the environment, and the occurrence of other symptoms.^[17] All of them can worsen asthma conditions, increase asthma symptoms, decrease lung function, increase episodes of asthma exacerbation, and increase morbidity as well as treatment cost.[18] These will be associated with negative social effects, such as lack of confidence, decreased quality of life, absenteeism in work or school, negative social stigma, and the destruction of family or friend relationships. All these conditions result in a negative feedback circle that will worsen psychological disorders.[18,19]

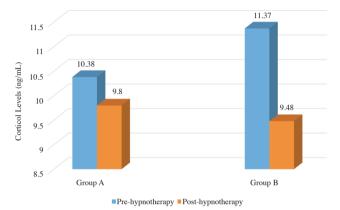


Figure 4. Effects of hypnotherapy on serum cortisol levels.

Table 4. Effect of hypnotherapy on serum IL13 levels.

		IL-13 levels (pg/mL)		
Group	n	Median (minimum-maximum)	p value	
Post-hypnotherapy (A2) Before hypnotherapy (A3)	15 15	1.65 (0.30-24.52) 4.58 (0.74-20.54)	0.132*	

^{*}Wilcoxon test

The results demonstrated that hypnotherapy significantly improved the standard therapy response in psychogenic asthma patients. Our findings suggest that standard therapy alone with short-term (six sessions) hypnotherapy for 6 weeks, improved asthma control. Moreover, based on our study, the uncontrolled and partly controlled asthma

Table 5. Effect of hypnotherapy on serum IL17 levels.

		IL-17 levels (pg/mL)		
Group	n	Median (minimum-maximum)	p value	
Post-hypnotherapy (A2) Before hypnotherapy (A3)	15 15	0.33 (0.10-3.36) 0.28 (0.07-1.57)	0.149*	

^{*}Mann Whitney test

Table 6. Detection limits of the ELISA assays for norepinephrine, cortisol, IL-13 and IL-17.

Reagent Kit	Range	Limit of detection
Human IL-13 ELISA Kit (ab100553)	0.16 pg/ml - 40 pg/ml	0.15 pg/ml
ARG80437 Human 3 CAT (Adrenaline + Noradrenaline + Dopamine) ELISA Kit	NAD: 5 - 1000 ng/ml	0.04 pg/ml
Cortisol ELISA Assay Kit (Eagle Biosciences)	0.5–60 μg/dL	0.4 µg/dL
Interleukin-17A Human ELISA (BioVendor)	1.6–100 pg/ml	0.5 pg/ml

became controlled after six hypnotherapy sessions by hypnotherapy. Clinical symptoms improved after hypnotherapy.

Psychosocial stress is a risk factor for asthma through endocrinological, neurological, immunity, and behavioral processes.[20] Therefore, emotional factors such as stress can disarrange the physiological pathway, including airway autonomic control, endocrinological system, and immune function, which cause late exacerbate an asthma attack.[16] Psychosocial stress leads to the shifting of inflammatory response toward Th-2 lymphocytes in line with the charac- teristics of asthma.^[21] Once hypnotherapy is initiated in asthma patients, these subjects will be in a hypnotic state to experience the reaction shift so that allergic response is inhibited and the bronchial inflammation changes.[11] Besides, the airway constriction mechanism involves inflammation and the cholinergic (vagal) tract.[14] Initiating hypnotherapy will influence non-adrenergic and non-cholinergic nervous systems, which are found in airway smooth muscle resulting in bronchodilation in a long term.[22]

Our study showed that hypnotherapy could increase the norepinephrine level of psychogenic asthma patients. Norepinephrine is the main catecholamine released by the sympathetic nervous system and significantly influences lymphocytes, including T cells, B cells, and natural killer cells, that play an important role in the pathogenesis of asthma.^[23] Norepinephrine binds to adrenergic receptors on the surface of various immune cells. The beta-2 adrenergic receptor is the main receptor of T and B cells, directly modulating the cellular activity through norepinephrine.24 This signal is one of the mechanisms in which the nervous system regulates our immune system.^[22,23] Beta-2 adrener gic receptor is expressed by Th-1 but not by Th-2.^[25]

Norepinephrine functions as a hormone and neurotransmitter.^[24] Norepinephrine levels were found to be decreased in depressive individuals.^[26] Thus, many efforts have been instituted to increase the norepinephrine level. ^[27] Hypnotherapy can reduce the stress levels so that norepinephrine levels improved. This is in line with the research of Sutanto et al.,^[28] which showed that hypnotherapy significantly increased the norepinephrine levels in psychogenic asthma patients.

Our analysis of other stress mediators revealed that

hypnotherapy, though not statistically significant, could lower the serum cortisol level of psychogenic asthma patients. This finding is in agreement with the study of Kasos et al., [29] which stated that hypnosis could lower the HPA axis mediator, including cortisol. The modulation of the neuroendocrine modulator by hypnosis, like cortisol, tends to have a different effect on Th-1 and Th-2. Hypnotherapy provides a beneficial response to the non-(NANC) system.[30] adrenergic non-cholinergic Catecholamine that is released by the adrenal medulla and neurotransmitter from the NANC system induce bronchodilation with relaxation of bronchial smooth muscle. The NANC system facilitates nitric oxide (NO) diffusion from the epithelial cell, eventually producing an increased fractional exhaled nitric oxide.[31]

This current study demonstrated the carryover effect of hypnotherapy; so the cortisol level increased again after the hypnotherapy was stopped. The cortisol levels were low during hypnotherapy. [9] The cortisol level decreased significantly after the emotional state is controlled using hypnotherapy. Despite the limited evidence, it has been demonstrated that hypnosis has the potential to modulate the HPA axis. On the other hand, the significance of hypnosis in lowering cortisol levels has not been proven. [30] This finding is supported by the study of Varga and Kekecs, [32] which identified that the change in the cortisol level after hypnotherapy was not correlated with patient's susceptibility to hypnosis but by relational experience instead.

Our analysis revealed that implementation of hypnotherapy six times, though not statistically significantly, lowered IL-13 levels. This insignificant decrease was also seen in IL-17 levels. In general, stress mediators involving in the control of asthma had a negative correlation with norepinephrine and a weak positive correlation with the cortisol level. Meanwhile, the pro-inflammatory cytokines associated with asthma control level showed a positive correlation with serum IL-13 and a negative and weak correlation with serum IL-17 levels. Both stress mediators and serum IL-13 pro-inflammatory cytokine contributed to the asthma in 3.8% of the patients. The mean level of norepinephrine was positively correlated with hypnotherapy, while the mean cortisol level had a weak negative correlation with the IL-17 level.

Conclusion

Asthma is a heterogeneous disease with various underlying disease processes. Psychogenic asthma patients have poor asthma control levels and increased levels of stress and inflammation mediators, which all play roles in the pathogenesis of asthma. Good psychogenic management using hypnotherapy can lower the SCL-90 score significantly and improve asthma control level, decrease levels of stress, and inflammation mediators.

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