Am J Transl Res 2023;15(2):1360-1366
www.ajtr.org /ISSN:1943-8141/AJTR0145734

Original Article

Therapeutic effect of modified Xiaoqinglong Decoction on cough-variant asthma and immunological functioning in children

Jun Li, Ying Han

Department of Integrated Traditional Chinese and Western Medicine, Wuhan Children's Hospital (Wuhan Maternal and Child Healthcare Hospital), Tongji Medical College, Huazhong University of Science & Technology, Wuhan 430010, Hubei, China

Received August 3, 2022; Accepted December 20, 2022; Epub February 15, 2023; Published February 28, 2023

Abstract: Objective: To investigate the effect of modified Xiaoqinglong Decoction on cough variant asthma (CVA) and immunological functioning in children. Methods: In this is retrospective analysis, 122 children with CAV admitted to our hospital from Mar. 2021 to Mar. 2022 were divided into an observation group (n=61) and a control group (n=61) according to treatment methods. The control group received fluticasone propionate inhalation aerosol, and the observation group additionally received Xiaoqinglong Decoction. The therapeutic efficacy in the two groups was compared after 8 weeks of treatment. The comparison indictors included scores of daytime and nighttime cough, pulmonary function, fractional exhaled nitric oxide (FeNO), eosinophil count, inflammatory response (interleukin-4 (IL-4), tumor necrosis factor-α (TNF-α) and macrophage inflammatory protein ((MIP)-1α), immunoglobulin (Ig)) level and adverse reactions. Results: The overall response rate of children with CVA in the observation group was higher than that in the control group (*P<0.05*). After treatment, the scores of daytime and nighttime cough in the observation group were lower than those in the control group (*P<0.05*). The Forced Vital Capacity (FVC), peak expiratory flow (PEF) and FEV1 (Forced Expiratory Volume)/FVC of the observation group were higher than those in the control group (*P<0.05*). The FeNO and eosinophil count in the observation group were lower than those in the control group (*P<0.05*). The serum IL-4 was higher, while TNF-α and MIP-1α levels were lower in the observation group in the control group (*P<0.05*). The serum IgA, IgG and IgM levels in the observation group were higher than those in the control group (*P<0.05*). Conclusion: The modified Xiaoqinglong Decoction has a conspicuous effect on children with CVA. It helps to reduce cough symptoms, improve pulmonary function, reduce inflammatory response and improve immunological functioning of children.

Keywords: Modified Xiaoqinglong Decoction, cough variant asthma in children, curative effect, immunological functioning

Introduction

Cough variant asthma (CVA) is a special type of asthma. Children with CVA usually have no obvious symptoms such as shortness of breath and wheezing. However, they often have recurrent and persistent coughing at night, accompanied by airway hyperresponsiveness and airway inflammation, which severely affects their physical and mental health [1, 2]. Epidemiological studies have shown that the incidence of CVA in children is increasing and may develop into typical asthma without proper treatment [3]. Hence, scientific and effective treatment methods are of great significance. At present, leukotriene receptor antagonists, bronchodilators and glucocorticoids are usually used in Western medicine to treat children with CVA. Although the cough symptoms can be effectively controlled, the children are prone to relapse after long-term use and drug withdrawal [4]. In recent years, it has been shown that traditional Chinese medicine can achieve good treatment efficacy in children with CVA [5]. Xiaoqinglong Decoction is a commonly used TCM prescription in clinical practice. It is capable of relieving exterior pain and heat, dispelling exterior cold, and warming the lungs and transforming fluid,

and it has a significant effect in treating phlegm, asthma and cough [6]. In order to further improve the treatment for CAV, this study, under the guidance of dialectical theory of TCM, adopted Xiaoqinglong Decoction for children with lung syndrome due to wind cold. In addition, this study discussed the effect of Xiaoqinglong Decoction on children with CAV and its influence on children's immune function from a mechanism perspective.

Data and methods

General data

In this retrospective analysis, 122 children with CVA admitted in Wuhan children's Hospital from Mar. 2021 to Mar. 2022 were enrolled. Diagnostic criteria of CVA were based on the *Guidelines for the Diagnosis and Prevention of Bronchial Asthma in Children* (2016 Edition) [7] and the *Guidelines for Diagnosis and Treatment of Pediatric Cough Variant Asthma by Traditional Chinese Medicine* [8]. The subjects were divided into an observation group (n=61) and a control group (n=61) according to different treatment methods. The control group was treated with western medicine (fluticasone propionate inhalation aerosol), and the observation group was treated with integrated traditional Chinese and western medicine (additional Xiaoqinglong Decoction). This study was approved by the Ethics Committee of Wuhan Children's Hospital.

Inclusion criteria

(1) Children met the diagnostic criteria of CVA [7, 8]. The syndrome differentiation was wind-cold attacking lung, and the disease condition varied from mild to moderate. (2) Children who were aged from 3 to 14 years. (3) Children who did not receive other treatment after onset.

Exclusion criteria

(1) Children who had poor compliance; (2) Children who had serious abnormalities of the hematopoietic system, liver, kidney, heart or other important organs; (3) Children who had cough caused by other diseases such as upper airway syndrome, tuberculosis and chronic pharyngitis. (4) Children who had mental illness. (5) Children with an allergic constitution.

Treatment methods

The control group was given fluticasone propionate inhalation aerosol (Glaxo Wellcome S.A.; H20130190) 100 μg/time, twice a day. The observation group was given additional Jianxian Qinglong Decoction orally, 180 ml each time, 2 times a day. The decoction was decocted from Zhimahuang 10 g, Baishao 10 g, Guizhi 12 g, Pinellia 10 g, Bitter almond 10 g, Poria 10 g, Dilong 10 g, Schisandra 6 g, Xin 3 g, dried tangerine peel 6 g, dried ginger 3 g and licorice 6 g. The treatment period was 8 weeks in both groups.

Criterion of efficacy

(1) Cure: The symptoms of cough and shortness of breath disappear completely, and no recurrence was found in 3 months; (2) Improved: Children's cough, shortness of breath and other symptoms improved; (3) Ineffective: The symptoms of cough and shortness of breath did not improve. Overall response rate (ORR) = (Cure cases + improve cases)/total number of cases.

Observation indicators

(1) Daytime and nighttime cough scores pre- and post-treatment were observed, 0 points: no cough; 1 point: occasional short cough; 2 points: frequent cough which slightly affects daily activities; 3 points: Frequent cough which seriously affects daily activities. A higher score referred to more serious cough. (2) The pulmonary function before and after treatment was measured by German Jaeger Master Screen IOS lung function instrument. (3) The changes of fractional exhaled nitric oxide (FeNO) and eosinophil count were observed before and after treatment. (4) The changes of inflammatory response were observed before and after treatment. Venous blood (3 mL) was collected before and after treatment and centrifuged at a speed of 2500 r/min at a centrifugal radius of 10 cm for 10 min, then the serum was collected. Interleukin-4 (IL-4), tumor necrosis factor -α (TNF-α) and macrophage inflammatory protein (MIP-1α) were determined by enzyme-linked immunosorbent assay using IL-4 ELISA kit (Abcam, ab215089), TNF-α ELISA kit (Abcam, ab181421) and MIP-1α ELISA kit (Shanghai Chuangqiu Biotechnology, China, HH-66), respectively. (5) The changes of immunoglobulin

Table 1. Comparison of efficacy between the two groups (%)

Group	Number of cases	Cured	Improved	Ineffective	Total response rate
Observation group	61	26 (42.62)	31 (50.82)	4 (6.56)	57 (93.44)
Control group	61	17 (27.87)	30 (49.18)	14 (22.95)	47 (77.05)
χ^2	-	-	-	-	6.517
P	-	-	-	-	0.011

Table 2. Comparison of scores of daytime and nighttime cough between the two groups before and after treatment (x ± s, points)

Group	Number of cases	Score of daytime coughs		Score of nighttime coughs	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	61	1.34±0.38	0.41±0.13*	1.97±0.41	0.84±0.14*
Control group	61	1.35±0.32	0.73±0.24*	2.01±0.34	1.25±0.19*
t	-	0.157	9.157	0.587	13.568
P	-	0.875	<0.001	0.559	<0.001

Note: Compared with before treatment, *$P<0.05$.

(Ig) level before and after treatment were observed. Venous blood (3 mL) was collected before and after treatment and centrifuged at a centrifugal radius of 10 cm and a centrifugal speed of 2500 r/min for 10 min. Then, the serum was collected, and IgA, IgG and IgM levels were determined by rate scattering turbidimetry. (6) The adverse reactions of the two groups were observed.

Statistical analysis

SPSS 25.0 was employed for data processing. Measurement data were represented by (x ± s), and t-test was used for comparison. Counting data were expressed as percentages, and χ^2 was used for comparison. *P<0.05* indicated statistical significance.

Results

Clinical data

The observation group consisted of 35 males and 26 females. The age of patients was from 3 to 14 years old, with an average age of (8.42±1.89) years. The course of disease was from 1 to 8 months, with an average of (4.51±1.28) months. In the control group, there were 34 males and 27 females. The age of patients was 3 to 13 years old, with an average age of (8.51±1.56) years. The course of disease was from 1 month to 9 months, with an average of (4.63±1.32) months. There was no significant difference in the general data between the two groups (*P>0.05*).

Comparison of efficacy

The ORR in the observation group was higher than that in control group (*P<0.05*), as shown in **Table 1**.

Comparison of daytime cough and nighttime cough scores

The post-treatment scores of daytime and nighttime cough were lower than those pre-treatment in both groups (*P<0.05*). Furthermore, the post-treatment scores in the observation group were lower than those in the control group (*P<0.05*) (**Table 2** and **Figure 1**).

Comparison of pulmonary function between the two groups

The post-treatment FVC, PEF and FEV1/FVC were higher than those pre-treatment in both groups (*P<0.05*). Moreover, the post-treatment FVC, PEF and FEV1/FVC in the observation group were higher than those in the control group (*P<0.05*) (**Table 3**).

Comparison of FeNO and eosinophil count

The post-treatment FeNO and eosinophil count were lower than those pre-treatment in both groups (*P<0.05*), and post-treatment FeNO and eosinophil count in the observation group were

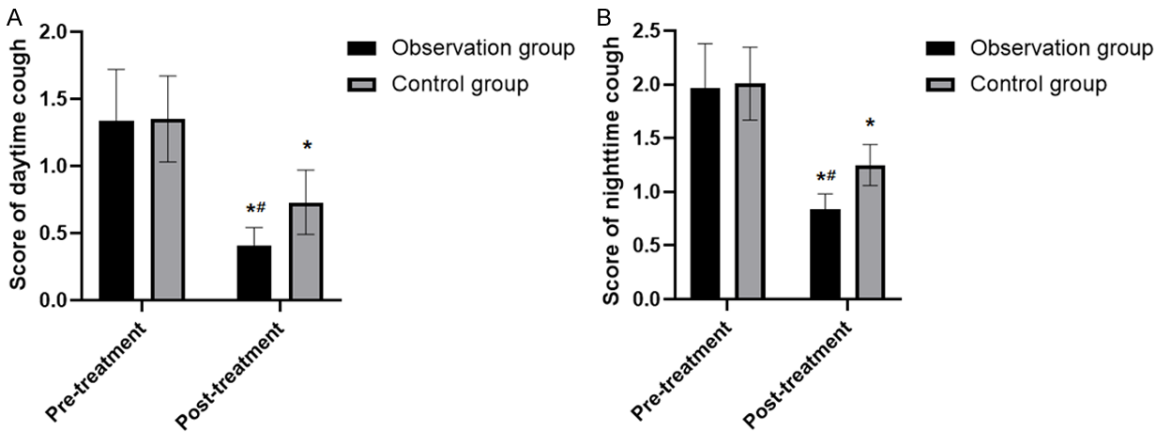

Figure 1. Comparison of scores of daytime and nighttime coughs between the two groups before and after treatment. A: Score of daytime cough; B: Score of nighttime cough. Compare with pre-treatment, $^{*}P<0.05$; Compare with the control group, $^{\#}P<0.05$.

Table 3. Comparison of pulmonary function between the two groups before and after treatment (x ± s)

Group	Number of cases	FVC (L)		PEF (L/min)		FEV1/FVC	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	61	1.83±0.21	2.68±0.17*	2.57±0.24	3.87±0.35*	74.32±5.41	86.52±4.23*
Control group	61	1.85±0.27	2.21±0.18*	2.54±0.31	3.19±0.27*	73.42±4.53	78.81±3.57*
t	-	0.457	14.826	0.598	12.015	0.996	10.879
P	-	0.649	<0.001	0.551	<0.001	0.321	<0.001

Note: Compared with before treatment, $^{*}P<0.05$. Forced Vital Capacity (FVC), peak expiratory flow (PEF) and FEV1 (Forced Expiratory Volume)/FVC.

Table 4. Comparison of FeNO and eosinophil count between the two groups before and after treatment (x ± s)

Group	Number of cases	FeNO (ppb)		Eosinophil count ($\times 10^9$/L)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	61	25.45±2.21	16.57±2.18*	0.50±0.12	0.14±0.06*
Control group	61	25.78±2.79	20.61±3.02*	0.52±0.15	0.27±0.09*
t	-	0.724	8.472	0.813	9.387
P	-	0.470	<0.001	0.418	<0.001

Note: Fractional exhaled nitric oxide (FeNO). Compared with before treatment, $^{*}P<0.05$.

lower than those in the control group ($P<0.05$) (**Table 4**).

Comparison of inflammatory response

After treatment, the serum IL-4 levels in both groups were higher than before treatment ($P<0.05$), while the serum TNF-α and MIP-1α levels were lower than before treatment ($P<0.05$). Also, the post-treatment serum IL-4 in observation group was higher, while TNF-α and MIP-1α levels were lower in the observation group than those in the control group ($P<0.05$) (**Table 5**).

Comparison of immunoglobulin degree

The post-treatment serum IgA, IgG and IgM levels were higher than those before treatment in both groups ($P<0.05$), and the post-treatment levels in the observation group were higher than those in the control group ($P<0.05$) (**Table 6**).

Discussion

The specific pathogenesis of CVA has not been fully clarified at the moment. It is believed that this disease is closely related to the inflamma-

Table 5. Comparison of inflammatory response between the two groups before and after treatment (x ± s)

Group	Number of cases	IL-4 (pg/ml)		TNF-α (μg/L)		MIP-1α (pg/ml)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	61	32.12±3.87	42.41±2.96*	12.32±1.56	5.65±1.28*	40.97±5.87	21.75±4.25*
Control group	61	30.84±4.56	37.74±4.65*	12.43±1.98	8.19±1.43*	42.21±7.45	29.84±6.64*
t	-	1.672	6.617	0.341	10.337	1.021	8.015
P	-	0.097	<0.001	0.734	<0.001	0.309	<0.001

Note: interleukin-4 (IL-4), tumor necrosis factor-α (TNF-α), macrophages inflammatory protein (MIP)-1α. Compared with before treatment, *$P<0.05$.

Table 6. Comparison of immunoglobulin levels between the two groups before and after treatment (x ± s)

Group	Number of cases	IgA (g/L)		IgG (g/L)		IgM (g/L)	
		Pre-treatment	Post-treatment	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment
Observation group	61	0.54±0.15	1.27±0.19*	6.98±1.21	11.32±1.78*	0.86±0.14	1.54±0.21*
Control group	61	0.57±0.16	0.89±0.21*	7.07±1.43	9.43±1.16*	0.87±0.18	1.06±0.13*
t	-	1.068	10.480	0.375	6.948	0.343	15.179
P	-	0.286	<0.001	0.708	<0.001	0.733	<0.001

Note: Compared with before treatment, *$P<0.05$.

tory components of various cells [9-11]. At present, the name CVA has not been clearly recorded in traditional Chinese medicine. The clinical characteristics of CVA include “dry cough”, “asthma cough”, “persistent cough”, “wind-induced cough” etc. Theoretically, Traditional Chinese Medicine regards CVA as an essential defect. Its internal causes are usually congenital deficiency, insufficiency of kidney, spleen, and lungs, and the loss of body fluids to produce phlegm [12]. The liver often has excess to form internal wind. The external causes are often unbalanced diet, exogenous pathogenic Qi, etc. If the internal and external factors are combined, spasticity of spittoon and stagnation of qi will result in the airway, and the abnormal rise and fall of lung qi will result in cough [13]. The basic mechanism of CVA is lung attacked by wind cold, phlegm retention, pulmonary qi loss and acute airway contracture. Prolonged coughing damages the qi of lungs, which makes the lung fails to clear and purify, and blocks the water channel, so that after drinking water, the body fluids do not disperse. Lung qi is depleted, and the functions of external defenses are out of balance, so the body is easily re-sensitizes to external pathogens such as wind and cold. Cold drinks can compress the lungs and block the airway, and therefore result in recurring cough [14]. Therefore, the treatment should be to warm the lungs to disperse cold, and to relieve the cough by drinking. Xiaoqinglong Decoction can relieve lung asthma, sweat, and relieve the exterior, and reduce swelling due to the effect of diuresis. Paeonia lactiflora can soften the liver and tighten the lungs. Cinnamon twig with warm water can disperse cold and relieve the body. Method Pinellia dispels phlegm and dissipates stagnation, stops cough, dries dampness and resolves phlegm. Bitter almonds reduce qi and relieve cough. Poria spleen invigorates the spleen and resolves phlegm, diuresis and dampness. Dilong can clear heat, calm panic and relieve asthma and diuresis. Schisandra can astringe the lungs and relieve cough. Asarum dispels wind and cold, and warms the lung. Dried tangerine peel moistens phlegm and strengthens spleen. Dried ginger disperses cold, warms the lung, and restores the yang to dredge the meridians. Zhigancao reconciles various medicines, relieves cough and asthma, and strengthens the spleen and qi [15, 16]. Modern pharmacological studies have shown that Xiaoqinglong Decoction has strong anti-asthmatic, anti-cough, anti-inflammatory and anti-allergic effects. It can inhibit the release of inflammatory mediators, has significant bronchial dilatation effect, and can antagonize the effect of histamine on bronchoconstriction [17]. This study showed that the total efficacy of the observation group was higher than that of the control group, which proved that Xiaoqinglong Decoction can improve the curative effect in children. The scores

of daytime and nighttime cough in the observation group after treatment were lower than those in the control group, indicating that modified Xiaoqinglong Decoction can reduce the daytime and nighttime coughs in children. The post-treatment FVC, PEF and FEV1/FVC of the observation group were higher than those of the control group, suggesting that the modified Xiaoqinglong Decoction can improve the lung function of children. The post-treatment FeNO and eosinophil count in the observation group were lower than those in the control group, demonstrating that Xiaoqinglong Decoction could reduce FeNO and eosinophil count.

Chronic airway inflammation is a key in the pathogenesis of CVA. IL-4 is an important anti-inflammatory cytokine in the inflammatory response. It can also extensively inhibit the expression of other pro-inflammatory factors and inflammatory mediators, and promote the secretion of anti-inflammatory factors, which is conducive to correcting the balance of pro-inflammatory/anti-inflammatory factors [18]. TNF-α enhances the expression of IL-like inflammatory factors in human lung fibroblasts through Akt and JNK signaling, promoting the occurrence of airway inflammatory diseases [19]. MIP-1α is a beta chemokine secreted by monocytes and macrophages. MIP-1α can lead to airway inflammation by helping the smooth movement of eosinophils to the airway, and promote the infiltration of smooth muscle by mast cells, thereby aggravating inflammation [20]. According to this study, the serum IL-4 levels in the two groups after treatment were higher than those before treatment, while the TNF-α and MIP-1α levels were lower than those before treatment. Also, the post-treatment serum IL-4 level was higher, while TNF-α and MIP-1α levels were lower in the observation group than those in control group. Thi indicated that Xiaoqinglong Decoction can reduce inflammation by increasing serum IL-4 and decreasing the levels of TNF-α and MIP-1α. Low immune function is closely related to childhood asthma [21]. IgA, IgG and IgM are important indicators to evaluate immune function [22]. This study indicated that IgA, IgG and IgM levels in the observation group after treatment were higher than those in the control group, which showed that the modified Xiaoqinglong Decoction could improve the immune function of children. Therefore, we believe that the mechanism of Xiaoqinglong Decoction in the treatment of CAV may be related to the reduction of the inflammatory response and the improvement of immune function of children.

However, the sample size included in this study was limited, and the research on the mechanism of treatment was not in-depth. Therefore, it is necessary to further expand the sample size and conduct in-depth mechanism analysis in the later study.

Modified Xiaoqinglong Decoction has a conspicuous effect on children with CVA, which can reduce cough symptoms, improve pulmonary function, reduce inflammatory response and improve immunological functioning of children.

Acknowledgements

This work was supported by the Scientific Research Project of Traditional Chinese Medicine of Wuhan Health Commission (No.: WZ22B02).

Disclosure of conflict of interest

None.

Address correspondence to: Jun Li, Department of Integrated Traditional Chinese and Western Medicine, Wuhan Children's Hospital, No. 100 Hong Kong Road, Jiang'an District, Wuhan 430010, Hubei, China. Tel: +86-027-82433165; E-mail: 13477000522@163.com

References

[1] Enseki M, Nukaga M, Tadaki H, Tabata H, Hirai K, Kato M and Mochizuki H. A breath sound analysis in children with cough variant asthma. Allergol Int 2019; 68: 33-38.

[2] Zou JR, Wang WL and Xie XH. Analysis of the effect of moxibustion combined with antisensitive and antispasmodic decoction on immunoglobulin in children with cough variant asthma. Minerva Pediatr 2022; 74: 90-92.

[3] Rybka-Fraczek A, Dabrowska M, Grabczak EM, Bialek-Gosk K, Klimowicz K, Truba O and Krenke R. Does bronchial hyperresponsiveness predict a diagnosis of cough variant asthma in adults with chronic cough: a cohort study. Respir Res 2021; 22: 252.

[4] Bruton A, Lee A, Yardley L, Raftery J, Arden-Close E, Kirby S, Zhu S, Thiruvothiyur M, Webley F, Taylor L, Gibson D, Yao G, Stafford-Watson M, Versnel J, Moore M, George S, Little P, Djukanovic R, Price D, Pavord ID, Holgate ST and Thomas M. Physiotherapy breathing re-

training for asthma: a randomised controlled trial. Lancet Respir Med 2018; 6: 19-28.
[5] Corren J, Castro M, O'Riordan T, Hanania NA, Pavord ID, Quirce S, Chipps BE, Wenzel SE, Thangavelu K, Rice MS, Harel S, Jagerschmidt A, Khan AH, Kamat S, Maroni J, Rowe P, Lu Y, Amin N, Pirozzi G, Ruddy M, Graham NMH and Teper A. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. J Allergy Clin Immunol Pract 2020; 8: 516-526.
[6] Lee-Sarwar KA, Kelly RS, Lasky-Su J, Zeiger RS, O'Connor GT, Sandel MT, Bacharier LB, Beigelman A, Laranjo N, Gold DR, Weiss ST and Litonjua AA. Integrative analysis of the intestinal metabolome of childhood asthma. J Allergy Clin Immunol 2019; 144: 442-454.
[7] Subspecialty Group of Respiratory Diseases, Society of Pediatrics, Chinese Medical Association; Editorial Board, Chinese Journal of Pediatrics. Guidelines for diagnosis and prevention of bronchial asthma in children (2016 edition). Chin J Pediatr 2016; 54: 167-181.
[8] Chung Y, Huang TY, Liao YH and Kuo YC. 12-week inspiratory muscle training improves respiratory muscle strength in adult patients with stable asthma: a randomized controlled trial. Int J Environ Res Public Health 2021; 18: 3267.
[9] Kunc P, Fabry J, Zatko T, Grendar M, Tatar M and Pecova R. Cough reflex sensitivity and fractional exhaled nitric oxide in children with asthma. Physiol Res 2020; 69: 455-461.
[10] Goorsenberg AWM, d'Hooghe JNS, Srikanthan K, Ten Hacken NHT, Weersink EJM, Roelofs JJTH, Kemp SV, Bel EH, Shah PL, Annema JT and Bonta PI; TASMA research group. Bronchial thermoplasty induced airway smooth muscle reduction and clinical response in severe asthma. The TASMA randomized trial. Am J Respir Crit Care Med 2021; 203: 175-184.
[11] Chen LJ, Huang MQ and Xie NL. The effect of montelukast sodium plus budesonide on the clinical efficacy, inflammation, and pulmonary function in children with cough variant asthma. Am J Transl Res 2021; 13: 6807-6816.
[12] Zhang O, Minku LL and Gonem S. Detecting asthma exacerbations using daily home monitoring and machine learning. J Asthma 2021; 58: 1518-1527.
[13] Sanz-Santiago V, Diez-Vega I, Santana-Sosa E, Lopez Nuevo C, Iturriaga Ramirez T, Vendrusculo FM, Donadio MVF, Villa Asensi JR and Pérez-Ruiz M. Effect of a combined exercise program on physical fitness, lung function, and quality of life in patients with controlled asthma and exercise symptoms: a randomized controlled trial. Pediatr Pulmonol 2020; 55: 1608-1616.
[14] Duruturk N, Acar M and Doğrul MI. Effect of inspiratory muscle training in the management of patients with asthma: a randomized controlled trial. J Cardiopulm Rehabil Prev 2018; 38: 198-203.
[15] Thorsen J, Stokholm J, Rasmussen MA, Mortensen MS, Brejnrod AD, Hjelmsø M, Shah S, Chawes B, Bønnelykke K, Sørensen SJ and Bisgaard H. The airway microbiota modulates effect of azithromycin treatment for episodes of recurrent asthma-like symptoms in preschool children: a randomized clinical trial. Am J Respir Crit Care Med 2021; 204: 149-158.
[16] Toennesen LL, Meteran H, Hostrup M, Wium Geiker NR, Jensen CB, Porsbjerg C, Astrup A, Bangsbo J, Parker D and Backer V. Effects of exercise and diet in nonobese asthma patients-a randomized controlled trial. J Allergy Clin Immunol Pract 2018; 6: 803-811.
[17] Cabana MD, McKean M, Caughey AB, Fong L, Lynch S, Wong A, Leong R, Boushey HA and Hilton JF. Early probiotic supplementation for eczema and asthma prevention: a randomized controlled trial. Pediatrics 2017; 140: e20163000.
[18] McDonald VM, Clark VL, Cordova-Rivera L, Wark PAB, Baines KJ and Gibson PG. Targeting treatable traits in severe asthma: a randomised controlled trial. Eur Respir J 2020; 55: 1901509.
[19] Pourdowlat G, Hejrati R and Lookzadeh S. The effectiveness of relaxation training in the quality of life and anxiety of patients with asthma. Adv Respir Med 2019; 87: 146-151.
[20] Brustad N, Eliasen AU, Stokholm J, Bønnelykke K, Bisgaard H and Chawes BL. High-dose vitamin D supplementation during pregnancy and asthma in offspring at the age of 6 years. JAMA 2019; 321: 1003-1005.
[21] Dupin C, Belhadi D, Guilleminault L, Gamez AS, Berger P, De Blay F, Bonniaud P, Leroyer C, Mahay G, Girodet PO, Raherison C, Fry S, Le Bourdellès G, Proust A, Rosencher L, Garcia G, Bourdin A, Chenivesse C, Didier A, Couffignal C and Taillé C. Effectiveness and safety of dupilumab for the treatment of severe asthma in a real-life French multi-centre adult cohort. Clin Exp Allergy 2020; 50: 789-798.
[22] Miller RL, Grayson MH and Strothman K. Advances in asthma: new understandings of asthma's natural history, risk factors, underlying mechanisms, and clinical management. J Allergy Clin Immunol 2021; 148: 1430-1441.