Cellular and Molecular Biology
E-ISSN : 1165-158X / P-ISSN : 0145-5680
www.cellmolbiol.org

Original Research

Expressions of IL-12 and its receptors in patients with lumbar disc herniation and their relationship with clinical efficacy

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Received December 05, 2019; **Accepted** August 24, 2020; **Published** October 31, 2020

Doi: http://dx.doi.org/10.14715/cmb/2020.66.7.2

Abstract: This study aimed to explore the expressions of interleukin-12 (IL-12) and its receptors IL-23R and IL12RB2 in patients with lumbar disc herniation (LDH) before and after treatment and their relationship with clinical efficacy. A total of 172 LDH patients undergoing surgical treatment in Wuhan Third Hospital, Tongren Hospital of Wuhan University were enrolled as the study group, and 170 healthy subjects as the control group. 5 mL of fasting venous blood was taken before surgery (T0), 1 d (T1), 3 d (T2), 5 d (T3) and 7 d (T4) after treatment respectively. The concentrations of IL-12, IL-23R and IL12RB2 in the two groups were detected, and the correlation between them and the treatment duration and clinical efficacy was analyzed. The study group showed significantly higher serum IL-12, IL-23R and IL12RB2 than the control group before treatment ($P < 0.001$). In the study group, IL-12, IL-23R and IL-12RB2 were the lowest at T4 ($P < 0.001$), followed by T3 ($P < 0.001$). There was no significant difference in IL-23R at T1 and T0 ($P > 0.050$), and in IL12RB2 at T1 and T2 ($P > 0.050$). Spearman rank correlation showed that IL-12, IL-23R, IL12RB2 were negatively correlated with treatment duration in the study group ($P < 0.001$), and were positively correlated with clinical efficacy ($P < 0.001$). In conclusion, the concentrations of serum IL-12, IL-23R and IL12RB2 in LDH patients are significantly higher than those in normal controls. Moreover, the concentrations are closely related to the rehabilitation of patients and are expected to become therapeutic targets for LDH.

Key words: Lumbar disc herniation; IL-12; IL-23R; IL12RB2.

Introduction

Lumbar disc herniation (LDH) is one of the most common spinal diseases in clinical practice. After the intervertebral disc components have different degrees of degenerative diseases, the intervertebral disc fibers rupture occurs due to the interference of external factors, and the nucleus pulpous tissues protrude from the rupture to compress the spinal nerve roots and the spinal cord, leading to the occurrence of LDH (1, 2). LDH is common in middle-aged and elderly people with an annually increasing incidence due to population aging (3). A survey shows that in recent years, spinal degeneration has been greatly increased, and the incidence rate of various spinal diseases has been rising (4). The fast-paced and stressful social life leads to a significantly younger trend of the onset of LDH (5). LDH usually causes lumbago, numbness of limbs and muscle paralysis, even defecation dysfunction and lower limb paralysis in severe cases, seriously affecting people's normal life (6, 7). For mild patients, conservative treatment is advocated clinically, while for severe patients, surgical treatment is required (8, 9). However, both methods have long treatment cycles, and surgical treatment is difficult to be operated. Besides, there is a great risk of infection and nerve injury, aggravating the sequelae of patients (10). With the severe challenges brought by the increasing LDH, researchers at home and abroad are constantly committed to exploring effective methods, but no significant breakthrough has been made. However, more and more researches recently point out that targeted therapy may become a breakthrough in the treatment of LDH (11, 12).

Interleukin-12 (IL-12), a cytokine in the chemokine family, has a strong regulatory effect on immune response and cell activation (13). At present, studies have proved that IL-12 is closely related to the occurrence and development of various diseases (14, 15). Moreover, a study by Park et al. (16) suggests that IL-12 may be closely related to LDH, but no further experimental analysis has been carried out. In this study, we hypothesize that IL-12 is closely related to LDH, and further analyze whether its receptors affect LDH, in order to explore the significance of IL-12 in the process of LDH and provide new ideas for its future clinical treatment.

Materials and Methods

A total of 172 LDH patients admitted to Wuhan Third Hospital, Tongren Hospital of Wuhan University from January 2017 to January 2019 were enrolled as the study group, including 104 males and 68 females, aged 57-70 years with an average age of (61.9±8.6) years. In addition, 170 healthy subjects undergoing physical examinations were selected as the control group, including 108 males and 62 females, aged 55-72 years, with an average age of (60.5±9.2) years. This experiment was approved by the Ethics Committee of this hospital. All

the above research subjects signed informed consent forms.

Inclusion and exclusion criteria

Inclusion criteria: all patients in the study group met the clinical manifestations of LDH (17); patients were diagnosed with LDH by examinations in Wuhan Third Hospital, Tongren Hospital of Wuhan University; patients with complete case data; patients who agreed to cooperate and participate in the investigation of medical staff. Exclusion criteria: patients complicated with tumors; patients with other diseases that may affect the nervous system or immune system; patients complicated with other cardiovascular and cerebrovascular diseases; patients complicated with blood diseases; patients receiving other drugs or interventional therapy within 3 months before admission; patients with a physical disability; patients unable to take care of themselves; long-term bed rest patients; patients suffering from mental diseases; patients transferred to another hospital. Inclusion and exclusion criteria in the control group: patients undergoing physical examinations in this hospital; patients with normal examination results and without systemic diseases.

Methods

All patients in the study group received surgical treatment after diagnosis which was completed by senior orthopedic doctors in this hospital. 5 ml of fasting venous blood of the patients were extracted before surgery (T0), 1 d (T1), 3 d (T2), 5 d (T3) and 7 d (T4) after treatment, respectively. The blood was placed at room temperature for 30 min, then centrifuged for 10 min (4000rpm/min) to obtain serum. Enzyme-linked immunosorbent assay (ELISA) was used to detect the concentrations of IL-12 and its receptors IL-23R and IL12RB2 (IL-12 kit: Shanghai Xin Yu Biotech Co., Ltd., bsk00386; IL-23R kit: Nanjing Lifesci Biotechnology Co., Ltd., EK5774; IL12RB2 kit: Shanghai LMAI Biology Co., Ltd., LM-EL-4667). The operation process was carried out in a sterile environment in strict accordance with the instructions of the kits. The clinical curative effect of the patient was recorded. Cured: all clinical symptoms disappeared, and the patient could perform their daily activities normally; markedly effective: patient still suffered from a slight pain in waist and legs basically not affecting normal activities; effective: patients often suffered from pain in waist and legs affecting normal activities; ineffective: the clinical symptoms of the patients did not change or even worsen. The correlation between IL-12, IL-23R, IL12RB2 and therapeutic effect was analyzed.

Statistical methods

SPSS24.0 statistical software (Shanghai Yuchuang Network Technology Co., Ltd.) was used for statistical analysis. Graphpad8 (Shenzhen Soft Head Software Technology Co., Ltd.) was used to draw all figures and double-check the results. Counting data such as gender and living environment were expressed in the form of (rate), and the chi-square test was used for comparison between groups. Measurement data such as IL-12 and IL-23R concentrations were expressed by (mean±standard deviation). The comparison between groups adopted *t*-test, the comparison among multiple time points adopted repeated measures analysis of variance (ANOVA). The Bonferroni method was used for the test afterward. Spearman rank correlation was used for correlation analysis. The difference was statistically significant with $P < 0.050$.

Results

General data comparison

There was no significant difference in age, body mass index (BMI), blood routine test, gender, living environment, smoking, drinking and exercise habits ($P > 0.050$), proving the comparability between the two groups. However, it was found that the patients with waist injury history in the study group were significantly more than those in the control group ($P < 0.001$) (Table 1).

Comparison of IL-12, IL-23R, IL12RB2 concentrations between the two groups before treatment

Before treatment, serum IL-12 concentration in the study group was (18.84±4.17) pg/mL, significantly higher than that in the control group (4.16±2.09) pg/ml, $P < 0.001$. The serum IL-23R concentration in the study group was (3.87±0.16) pg/mL, also significantly higher than that in the control group (0.24±0.07) pg/ml, $P < 0.001$. The serum IL12RB2 concentration in the study group was significantly higher than that in the control group ((4.59±0.46) pg/mL *vs* (0.76±0.12) pg/ml), $P < 0.001$ (Figures 1).

Changes of IL-12, IL-23R and IL12RB2 concentrations in the study group

In the study group, the concentration of IL-12 at T0 was significantly lower than that at T1 but significantly higher than that at T2, T3 and T4 ($P < 0.001$), T2 was significantly higher than T3 and T4 ($P < 0.001$), T3 was higher than T4 ($P < 0.001$). The concentration of IL-12 in the study group at T0, T1, T2, T3 and T4 was significantly higher than that in the control group ($P < 0.001$). However, the concentration of IL-23R at T1 had no significant difference with that at T0 in the study group ($P > 0.050$), but was significantly higher than that at T2, T3 and T4 ($P < 0.001$), T2 was significantly higher than T3 and T4 ($P < 0.001$), T3 was higher than T4 ($P < 0.001$). The concentration of IL-23R in the study group at T0, T1, T2, T3 and T4 was significantly higher than that in the control group ($P < 0.001$). In the study group, the concentration of IL12RB2 at T1 had no significant difference with that at T2 ($P > 0.050$) but was significantly lower than that at T0, higher than that at T3 and T4 ($P < 0.001$), T3 was higher than T4 ($P < 0.001$). The concentration of IL12RB2 in the study group at T1, T2, T3 and T4 was significantly higher than that in the control group ($P < 0.001$) (Figure 2).

Correlation between IL-12, IL-23R, IL12RB2 concentrations and treatment duration in the study group

Spearman rank correlation showed that IL-12 concentration in the study group was negatively correlated with treatment duration (r=-0.775, $P < 0.001$); IL-23R was negatively correlated with treatment duration

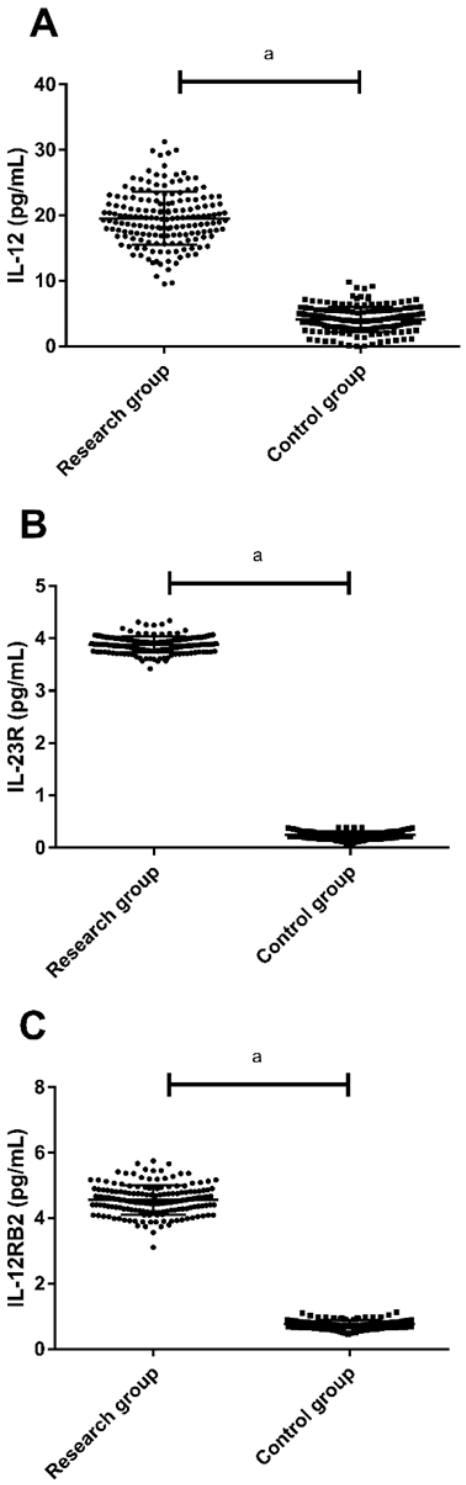

Figure 1. Comparison of serum IL-12, IL-23R and IL12RB2 between the two groups. A: The serum IL-12 concentration in the control group was significantly lower than that in the study group, aP < 0.001. B: The serum IL-23R concentration in the control group was significantly lower than that in the study group, aP < 0.001. C: The serum IL12RB2 concentration in the control group was significantly lower than that in the study group, aP < 0.001.

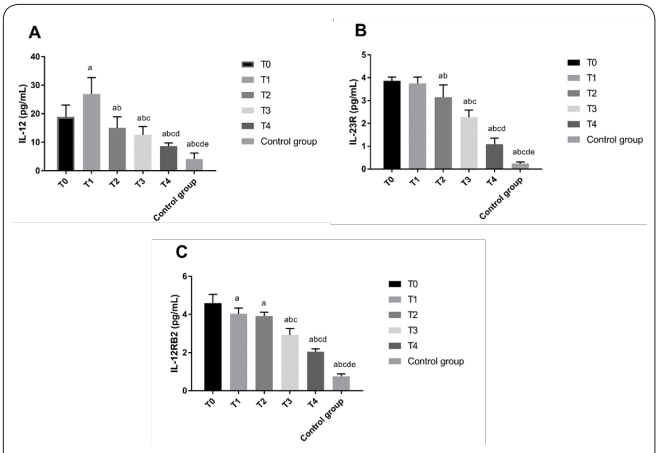

Figure 2. Changes of IL-12, IL-23R and IL12RB2 concentrations in the study group. A: Changes of IL-12 concentration in the study group a represents that compared with the concentration of IL-12 in the study group at T0, $P < 0.001$; b represents that compared with the concentration of IL-12 in the study group at T1, $P < 0.001$; c represents that compared with the concentration of IL-12 in the study group at T2, $P < 0.001$; d represents that compared with the concentration of IL-12 in the study group at T3, $P < 0.001$; e represents that compared with the concentration of IL-12 in the study group at T4, $P < 0.001$. The concentration of IL-12 at T0 was significantly lower than that at T1 but significantly higher than that at T2, T3 and T4 ($P < 0.001$), T2 was significantly higher than T3 and T4 ($P < 0.001$), T3 was higher than T4 ($P < 0.001$). The concentration of IL-12 in the study group at T0, T1, T2, T3 and T4 was significantly higher than that in the control group ($P < 0.001$).
B: Changes of IL-23R concentration in the study group a represents that compared with the concentration of IL-23R in the study group at T0, $P < 0.001$; b represents that compared with the concentration of IL-23R in the study group at T1, $P < 0.001$; c represents that compared with the concentration of IL-23R in the study group at T2, $P < 0.001$; d represents that compared with the concentration of IL-23R in the study group at T3, $P < 0.001$; e represents that compared with the concentration of IL-23R in the study group at T4, $P < 0.001$. The concentration of IL-23R at T1 had no significant difference with that at T0 in the study group ($P > 0.050$), but was significantly higher than that at T2, T3 and T4 ($P < 0.001$), T2 was significantly higher than T3 and T4 ($P < 0.001$), T3 was higher than T4 ($P < 0.001$). The concentration of IL-23R in the study group at T0, T1, T2, T3 and T4 was significantly higher than that in the control group ($P < 0.001$).
C: Changes of IL12RB2 concentration in the study group a represents that compared with the concentration of IL12RB2 in the study group at T0, $P < 0.001$; b represents that compared with the concentration of IL-23R in the study group at T1, $P < 0.001$; c represents that compared with the concentration of IL12RB2 in the study group at T2, $P < 0.001$; d represents that compared with the concentration of IL12RB2 in the study group at T3, $P < 0.001$; e represents that compared with the concentration of IL12RB2 in the study group at T4, $P < 0.001$. The concentration of IL12RB2 at T1 had no significant difference with that at T2 ($P > 0.050$) but was significantly lower than that at T0, higher than that at T3 and T4 ($P < 0.001$), T3 was higher than T4 ($P < 0.001$). The concentration of IL12RB2 in the study group at T1, T2, T3 and T4 was significantly higher than that in the control group ($P < 0.001$).

(r=-0.909, $P < 0.001$); IL12RB2 was negatively correlated with treatment duration (r=-0.903, $P < 0.001$). (Figure 3 and Table 2).

Correlation between clinical efficacy and IL-12, IL-23R, IL12RB2 concentrations in the study group

Of the 172 patients in the study group, 89 were cured, 62 were markedly effective, 14 were effective, and 7 were ineffective. The cured patients' IL-12, IL-23R and IL12RB2 were (8.97±2.82) pg/mL, (1.15±0.32) pg/mL and (2.28±0.25) pg/mL respectively. The levels in markedly effective patients were (11.89±1.86) can be

Table 1. General data comparison [n(%)].

	Study group (n=172)	Control group (n=170)	*t or* χ^2	*P*
Age			1.454	0.147
	61.9±8.6	60.5±9.2		
BMI (KG/cm^2)			0.844	0.399
	22.89±3.47	22.57±3.54		
Red blood cells (×10^{12}/L)			0.236	1.187
	3.94±0.17	3.92±0.14		
White blood cells (×10^9/L)			0.409	0.683
	8.27±1.26	8.33±1.45		
Platelets (×10^9/L)			1.441	0.151
	235.44±34.93	229.68±38.93		
Course of disease				
	2.16±0.57		0.341	0.559
Gender				
Male	104 (60.47)	108 (63.53)		
Female	68 (39.53)	62 (36.47)		
Living environment			0.891	0.345
Urban	134 (77.91)	125 (73.53)		
Rural	38 (22.09)	45 (26.47)		
Smoking			1.427	0.232
Yes	110 (63.95)	98 (57.65)		
No	62 (36.05)	72 (42.35)		
Drinking			1.701	0.192
Yes	88 (51.16)	75 (44.12)		
No	84 (48.84)	95 (55.88)		
Exercise habit			1.248	0.264
Yes	32 (18.60)	40 (23.53)		
No	140 (81.40)	130 (76.47)		
History of waist injuries			85.342	<0.001
Yes	104 (60.47)	21 (12.35)		
No	68 (39.53)	149 (87.65)		

Table 2. Correlation between IL-12, IL-23R, IL12RB2 and treatment duration in study group.

	IL-12	IL-23R	IL12RB2
r	-0.775	-0.909	-0.903
95%CI	-0.801~-0.746	-0.920~-0.896	-0.915~-0.889
P	<0.001	<0.001	<0.001

Table 3. Correlation between IL-12, IL-23R, IL12RB2 and therapeutic effect in study group.

	IL-12	IL-23R	IL12RB2
r	0.684	0.880	0.889
95%CI	0.592~0.758	0.840~0.910	0.851~0.917
P	<0.001	<0.001	<0.001

pg/mL, (1.94±0.20) pg/mL and (3.09±0.16) pg/mL. Those in effective patients were (14.36±2.05) pg/mL, (2.42±0.19) pg/mL and (3.39±0.25) pg/mL, and in ineffective patients were (16.89±2.89) pg/mL, (3.49±0.29) pg/mL and (4.02±0.33) pg/mL respectively. Spearman rank correlation showed that IL-12, IL-23R, IL12RB2 concentrations in the study group were positively correlated with clinical efficacy ($P < 0.001$) (Figure 4 and Table 3).

Discussion

LDH is one of the most common lumbar diseases caused by lumbar disc degeneration (18). It has been reported to be closely related to occupation, age, pregnancy and other reasons (19). With in-depth research, it is found that genetic and biomechanical changes may also cause LDH (20). IL-12 mainly produced by antigen-presenting cells (APCs) and B cells is a pro-inflammatory cytokine in the form of the heterodimer and

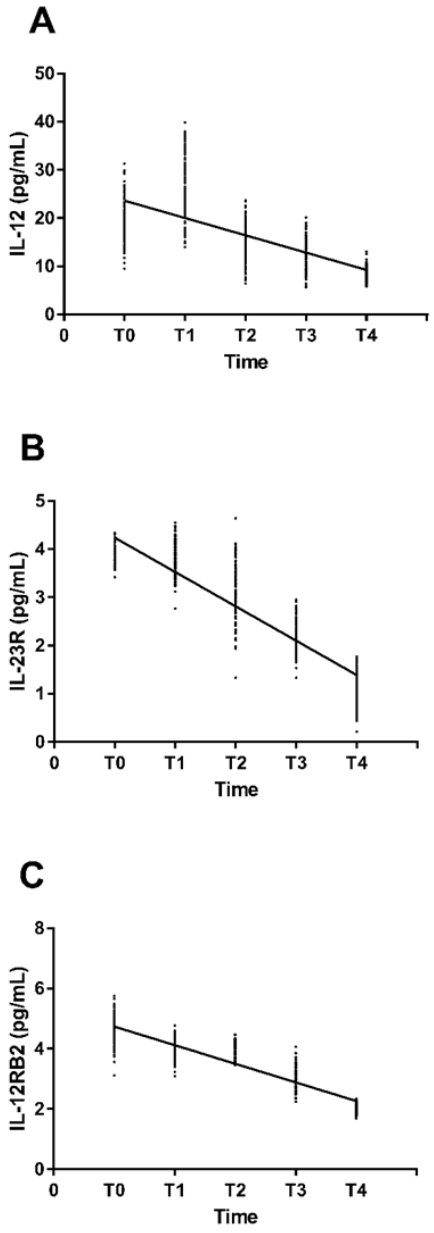

Figure 3. Correlation between IL-12, IL-23R, IL12RB2 concentrations and treatment duration in the study group. A: Spearman rank correlation showed that IL-12 was negatively correlated with treatment duration (r=-0.775, $P < 0.001$). B: Spearman rank correlation showed that IL-23R was negatively correlated with treatment duration (r=-0.909, $P < 0.001$). C: Spearman rank correlation showed that IL12RB2 was negatively correlated with treatment duration (r=-0.903, $P < 0.001$).

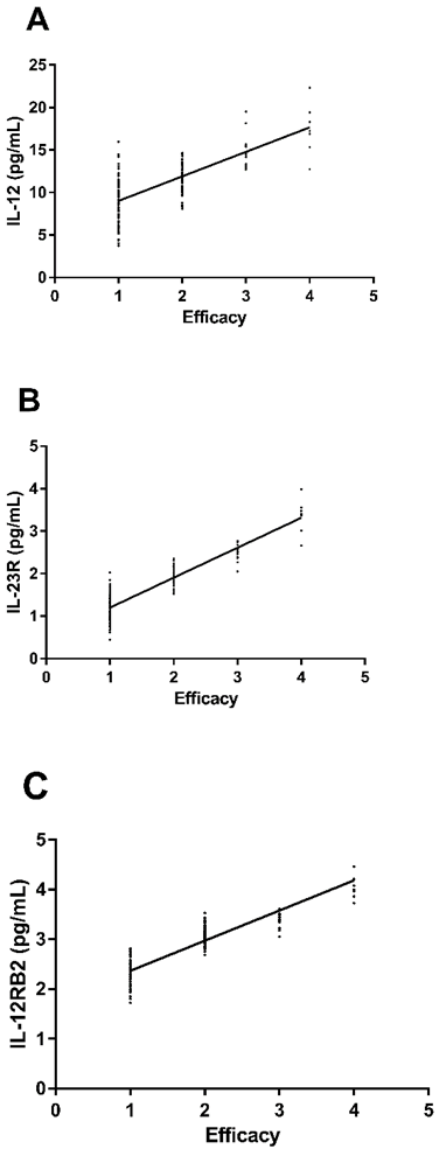

Figure 4. Correlation between IL-12, IL-23R, IL12RB2 concentrations and clinical efficacy in the study group. 1: cured; 2: markedly effective; 3: effective; 4: ineffective. A: Spearman rank correlation showed that IL-12 concentration in the study group was positively correlated with clinical efficacy (r=0.684, $P < 0.001$). B: Spearman rank correlation shows that IL-23R concentration in the study group was positively correlated with clinical efficacy (r=0.880, $P < 0.001$). C: Spearman rank correlation showed that IL12RB2 concentration in the study group was positively correlated with clinical efficacy (r=0.889, $P < 0.001$).

can be secreted out of the cells (21). Its receptors include IL-23R, IL12RB1, IL12RB2, IL6ST, and IL27R. Generally, IL-12 is considered to play a key role in regulating immune function and inflammatory function in parasitic diseases and chronic inflammation (22, 23). However, there are few studies on its role in LDH at home and abroad. Moreover, whether its receptors affect LDH has not been verified. Therefore, this study provided a reliable basis for targeted therapy of LDH by comparing IL-12, IL-23R and IL12RB2 between LDH patients and healthy people.

This study showed that the concentrations of IL-12, IL-23R and IL12RB2 in the study group were significantly higher than those in the control group before treatment, suggesting that IL-12, IL-23R and IL12RB2 may be involved in the occurrence and development of LDH. Aychaudhuri et al. (24) and Yang et al. (25) drew a consistent conclusion in the study of L-12, IL23R in spinal diseases, which supports our point of view. IL-12 promotes the proliferation of T and NK cells, enhances the cytotoxicity of T cells and the cytolytic activity of NK cells. Besides, it also affects inducing IFN-γ secretion and accelerating or causing the occurrence of nervous system diseases (26). LDH is closely related to nerve compression, which is presumed to be one of the key reasons for IL-12 to participate in this disease. During the occurrence and development of LDH, due to the rupture of intervertebral disc fibers, nucleus pulpous tissues protrude from the rupture or directly enter the vertebral canal, causing a series of nerve compression and nerve injury (27). Yao et al. (28) propose that the activity of T lymphocytes in LDH patients is signifi-

cantly higher than that in normal people. Therefore, it is speculated that IL-12 may increase the activity and toxicity of T lymphocytes by stimulating their proliferation, thus promoting IFN-γ secretion and causing nerve injury. Further analysis showed that IL-12 gradually decreased with the treatment duration, suggesting that IL-12 is closely related to the injury of patients. The concentration of IL-12 in the study group at T1 was significantly higher than that at T0. It is maybe that IL-12 not only has the effect of regulating immune function but also accelerates the inflammation. All functions of the patient receiving surgical treatment are in poor condition. In addition, the surgery may lead to severe lateral recess and spinal stenosis (non-muscular stenosis such as hypertrophy of ligamentum flavum) caused by calcification of protrusions, and lower limb muscular atrophy caused by vascular blood supply disorder after nerve root stimulation or compression (29). Therefore, the postoperative concentration of IL-12 increases significantly compared with that before surgery, which also reflects the difficulties in the clinical treatment of LDH and the importance of finding an effective targeted therapy. As one of the receptors of IL-12, IL-23R has also been proved to have a significant effect on the normal operation of immune function (30). A study claims that IL-23R is closely related to the occurrence of allergic rhinitis (31), while Chen et al. (32) believe that multiple single nucleotide polymorphism (SNP) sites in IL-23R may cause mandatory spondylitis. Therefore, we speculate that IL-23R also affects the normal function of cells through SNP sites in LDH, resulting in disorders of immune response and metabolic function, further causing chronic inflammation and tissue damage. IL12RB2 is mainly expressed on the surface of mitogens or IL-2-activated T cells and NK cells. On Th cell surface, IL12RB2 is only selectively expressed in IL-12-responsive cells. IFN-γ stimulation can up-regulate the transcription factor T-bet of Th1 cells, thus maintaining the continuous expression of IL12RB2 (33). Therefore, the role of IL12RB2 in LDH is also affected by IL-12, which further proves that the relationship between IL-12 and LDH may be established through IFN-γ. However, since IFN-γ in the study group was not detected in this experiment, further experiments are needed to confirm it. The correlation analysis showed that IL-12, IL-23R and IL12RB2 were positively correlated with clinical efficacy, indicating that IL-12, IL-23R and IL12RB2 are closely related to the rehabilitation of patients and are expected to become targets for the LDH treatment.

That not all IL-12 receptors were tested is one of the limitations of this experiment. Studies have suggested that LDH is related to the race of the patients. However, due to the limited experimental conditions, the subjects included in this study were all yellow people, so it is not excluded that the experimental results are occasional. Due to the short experimental cycle, it is impossible to evaluate the impact of IL-12, IL-23R and IL12RB2 on the prognosis of LDH. We will continuously improve and perfect the experimental design to conduct a more in-depth analysis of the role of IL-12 and its receptors in LDH.

To sum up, concentrations of serum IL-12 and its receptors IL-23R and IL12RB2 in LDH patients are significantly higher than those in normal controls. Moreover, the concentrations are closely related to the rehabilitation of patients and are expected to become therapeutic targets for LDH.

Acknowledgements
Not applicable.

Funding
No funding was received.

Availability of data and materials
The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions
XW wrote the manuscript. SZ and MF interpreted and analyzed the patient data. PW and HF designed the study and experimented. FB, TH and XD were responsible for the analysis and discussion of the data. All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of Wuhan Third Hospital, Tongren Hospital of Wuhan University. Patients who participated in this research signed informed consent and had complete clinical data. Signed written informed consent was obtained from the patients and/or guardians.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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