Observational Study

Conservative Treatment for Giant Lumbar Disc Herniation: Clinical Study in 409 Cases

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Free full manuscript: www.painphysicianjournal.com **Background:** There have been several recent reports of lumbar disc herniation (LDH) resorption; however, large sample studies are lacking, and the mechanism(s) underlying this phenomenon is unclear.

Objectives: To explore the feasibility and clinical outcomes of conservative treatment for giant LDH and to analyze the factors affecting the resorption of giant LDH.

Study Design: Observational study and original research.

Setting: This work was performed at a University Hospital of Traditional Chinese Medicine, Nanjing University of Traditional Chinese Medicine.

Methods: From January 2008 to December 2019, 409 patients with giant LDH who initially underwent nonsurgical treatment in our hospital were followed for 1–12 years to analyze the rate of surgical intervention, calculate the rate of resorption of protrusions, and the rate of excellent clinical outcomes.

Results: Eighty-nine of the 409 patients (21.76%) underwent surgery, while the remaining 320 patients (78.24%) constituted the non-surgical treatment group. The Japanese Orthopaedic Association (JOA) score in the 320 patients changed from 10.22 ± 3.84 points to 24.88 ± 5.69 points after treatment, and the rate of excellent outcomes was 84.06%. Among the 320 patients in the non-surgical treatment group, the protrusion percentage decreased from $70.08\pm30.95\%$ to $31.67 \pm 24.42\%$. One-hundred and eighty-nine patients (59.06%) had > 30% resorption of protrusions, and 81 patients (25.31%) had a significant resorption of protrusions of > 50%. Among 189 patients with resorption, the shortest resorption interval was 1 month, and the longest was 8 years, with 77 patients (40.74%) showing resorption within 6 months, 51 (26.98%) within 6–12 months, and 61 patients (32.28%) after 12 months.

Limitation: The main limitations are that all patients were from the same site, and there was a lack of multicenter randomized controlled trials with which to compare data.

Conclusions: Patients with giant LDH are less likely to develop progressive nerve injury and cauda equina syndrome if their clinical symptoms improve after treatment. As long as there is no progressive nerve injury or cauda equina syndrome, conservative treatment is preferred for giant disc herniation. Resorption is more likely with greater disc protrusions in the spinal canal. A ring enhancement bull's eye sign) around a protruding disc on enhanced magnetic resonance imaging is an important indicator of straightforward resorption.

Key words: Lumbar disc herniation, conservative treatment, giant, resorption, bull's eye sign

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n increasing number of patients experience lumbar disc herniation (LDH), which results in radiating pain in the lower extremities, as well as low back pain and neurological symptoms (1). In adults, the annual incidence of LDH is 5%, and the rate is gradually increasing (2). However, approximately 60%-90% of patients with LDH recover with conservative treatment (3). Even patients with a severely herniated disc or marked neurological deficits can be successfully treated with active conservative treatment (4). Guinto et al first reported a case of lumbar disc resorption after conservative treatment in 1984 (5). Since then, many scholars have reported similar findings regarding LDH resorption (6-10). Ahn et al evaluated the magnetic resonance (MR) images of 36 patients with LDH in clinical practice, and found that giant LDHs were the most prone to resorption (11). Macki et al observed through clinical trials that LDHs completely exposed to the epidural space were more likely to be reabsorbed. The authors also reported that the absorption rate of large types was higher than that of small- and medium-sized herniations, while resorption did not occur in patients with diffuse bulging and intervertebral space stenosis (12). Komori et al reported that the greater the degree of nucleus pulposus protrusion, the greater the extent of nucleus pulposus shrinkage after marked resorption (13). Orief et al observed resorption of the medullary nucleus of 6 large protrusions and speculated that with more abundant water content in the protrusion, it is easier for the protrusion to shrink after dehydration of the intervertebral disc tissue (14). Henmi et al (15) noted that large fragments of disc herniation were reduced more than small fragments and suggested that this might be due to larger disc fragments containing more water. Giant disc herniation is a special type of disc herniation. Numerous studies have assessed the natural history of lumbar disc lesions. Such studies, based on imaging changes, have shown that disc lesions can become smaller and even completely resolve, and this phenomenon is called LDH resorption (8,16,17). Lumbar magnetic resonance imaging (MRI) has become one of the most important imaging tools for the diagnosis of LDH. According to the method for measuring the percentage protrusion (18), we defined giant LDH as herniation of > 50% (19). Most spine surgeons recommend surgery for giant LDH. However, clinically, it has been observed that the greater the protrusion percentage of the disc into the spinal canal, the easier it is for resorption to occur. Approximately

20%–60% of patients with giant LDH experienced disc resorption after conservative treatment, and their symptoms resolved (10,20). Resorption is a natural process, and the larger the herniation, the greater the probability and degree of resorption. Numerous articles have reported that giant ruptured LDH is prone to resorption, but most studies were case reports, and some of the original studies had small sample sizes. We intend to follow-up a large sample of large LDH cases to further confirm the resorption rate. In this study, we retrospectively analyzed a group of patients with giant LDH over the past 12 years who initially underwent conservative treatment.

METHODS

General Data

From January 2008 to December 2019, after obtaining approval from our institutional Ethics Committee, patients with giant LDH were recruited from outpatient and inpatient clinics and informed of the study and the preferred method of non-surgical treatment. Inclusion criteria were as follows: (i) meeting the diagnostic criteria for giant LDH, with the location of the protruded segment and the symptoms being consistent, with radicular leg pain, a positive straight-leg raise test, and Lasegue's sign accompanied by decreased muscle strength and paresthesias in the corresponding parts of the legs. Lumbar MRI must also have shown a ruptured posterior longitudinal ligament with \geq 50% herniation; (ii) patients with Komori modified types 2 and 3; (iii) patients must have understood the study and volunteered to participate and agreed to initial non-surgical treatment. Exclusion criteria were as follows: (i) previous spinal surgery, scoliosis, spinal cord injury, tuberculosis, tumor, or cauda equina syndrome accompanied by nerve function impairment; (ii) rheumatism and immune system diseases such as combined rheumatic arthritis and ankylosing spondylitis; (iii) pregnancy or liver/kidney disease; and (iv) symptomatic osteoporotic fracture of the lumbar vertebra, serious spinal deterioration, lumbar spondylolisthesis, or protrusion of multiple segments.

Treatment Schedule

Conservative treatment involved: (1) Absolute bed rest for 2–6 weeks. (2) Taking the Traditional Chinese Medicine (TCM) preparation, Xiaosui Huahe decoction (roasted Astragalus 20 g, raw Astragalus 20 g, Angelica sinensis 10 g, rhizoma Atractylodis macrocephalae 10 g, Ligusticum wallichii 10 g, pawpaw 10 g, radix Stephaniae tetrandrae 10 g, Lumbricus 10 g, Brassica alba boiss 6 g, leech 6 g, and radix Clematidis 10 g) decocted in water and taken orally for 8-16 weeks; 72 patients also received acupuncture treatment. (3) For the first 1-2 weeks after an acute episode, if pain was not relieved, patients were permitted to take 0.1 g celecoxib twice daily. Surgical indications: conservative treatment with TCM ineffective (Japanese Orthopaedic Association (JOA) score < 16 points or improvement rate < 25%) after 3-6 months, or patients had progressive root symptoms or cauda equina nerve symptoms at any time during the treatment, and the size of the protrusion on MRI was unchanged or increased after re-examination. Operative procedures included simple resection of the nucleus pulposus, with decompression and fusion/non-fusion and internal fixation, with the choice of procedure depending on the patient's age, underlying cause of the lesion, and physiology of the lumbar vertebrae.

Therapeutic Evaluation

Clinical outcomes were evaluated using the JOA score, and the JOA improvement rate = (score after completion of treatment – score before treatment) / (29 – score before treatment) × 100 (the maximum possible score was 29). An improvement according to the JOA score of \geq 75% was classified as excellent, 50%–75% as good, 25%–50% as fair, and < 25% as poor.

Imaging Indicators

(1) Calculating protrusion percentage and absorption percentage (18): Setting the upper vertebral body wall after the halfway point of the trailing edge to the vertebral canal length as a (spinal canal diameter), and the prominence peak to vertebral canal wall distance

as b, the protrusion percentage = $[(a-b)/a] \times 100\%$ (Fig. 1). Absorption percentage = (protrusion percentage before treatment – protrusion percentage after treatment) / protrusion percentage before treatment.

(2) Komori improved typing (13): This is a method to predict whether resorption can occur based on initial MRI typing. We used this approach in this study, where we performed typing of the initial MRI of the enrolled patients. According to the degree of displacement of the protrusion on MRI, LDH was classified into 3 types. The key difference between type 2 and type 1 is that the continuity of the black line behind the herniated disc tissue is interrupted or absent with type 2, indicating that the protrusion has crossed the posterior longitudinal ligament. The key difference between type 3 and type 2 is that the herniated disc is above the height of the parent disc, and the greater the displacement, the more likely the protrusion will be absorbed. The 3 types are defined as follows: type 1, the black line behind the protruded disc is complete; type 2, the black line is interrupted or absent; and type 3, the herniated disc exceeds the height of the mother disc (Fig. 2).

(3) Bull's eye sign (the edge of the enhancement of the protrusion on enhanced MRI) (21): A herniated disc in the epidural space may cause an autoimmune

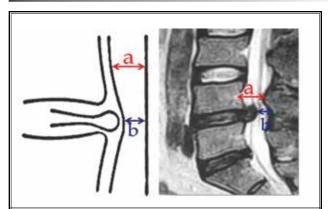
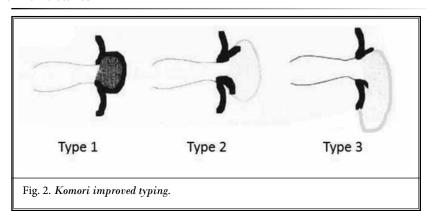


Fig. 1. MRI measurement of the protrusion percentage A: Length from the midpoint of the posterior margin of the upper vertebral body to the posterior wall of the spinal canal (diameter of the spinal canal); B: The distance from the highest point of the protrusion to the posterior wall of the spinal canal; protrusion percentage = $[(a-b)/a] \times 100\%$



response leading to an inflammatory response, with granulation tissue forming around the disc, which is characterized by annular enhancement and no enhancement of the central free disc. This finding is called a bull's eye sign (Fig. 3).

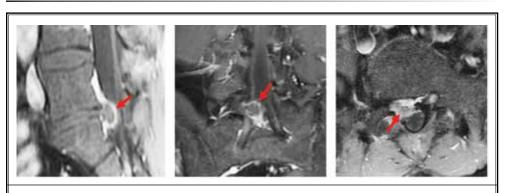
Follow-up

Patients were followed-up via an outpatient review, telephone inquiry, home visit, or other contact (Table 1). MRI examination was performed at the first and last visit, and the absorption percentage of the protrusion was calculated.

Statistical Method

Statistical analysis was performed using SPSS 20.0 statistical software (IBM Corp., Armonk, NY). Measurement data such as JOA score and protrusion percentage were compared by Student t test for matched data, whereas enumeration data, such as improvement according to JOA score, were compared by the χ^2 test or the Fisher exact probability test. *P* < 0.05 was considered statistically significant for all statistical tests.

RESULTS



Demographics

A total of 409 patients with giant LDH were included in the study. Patients' clinical characteristics are shown in Table 2, and the range and mean values for age, course of disease, follow-up, and MRI re-evaluation are shown in Table 3.

Fig. 3. Circumferential enhancement around sagittal, coronal, and axial protrusions (bull's eye sign)

							Study	y Peri	od								
m ••••	Enrollment	Treatment (month)			Follow-up (year)												
Timepoint	0	0-3	3-6	6-9	9-12	1	2	3	4	5	6	7	8	9	10	11	12
Essential information	×																
Screening	×																
Informed consent	×																
Treatment:																	
Bed or waistline		×															
ТСМ		×	×														
Painkiller		×															
Therapeutic evaluation:											•						
JOA score		×	×	×	×	×		×		×							
protrusion percentage		×		×		×		×		×							
Komori type		×															
MRI																	
Enhanced MRI		×		×		×		×		×							
Adverse events:																	
Cauda equina syndrome																	
Operation																	

Table 1. Follow-up registration.

Efficacy of Conservative Versus Surgical Treatment

During the follow-up period for the 409 patients, 89 patients (21.76%) chose surgical treatment, while the other 320 patients (78.24%) recovered with conservative treatment (Fig. 4). The clinical symptoms of the 320 conservatively treated patients were effectively improved, and the combined excellent and good outcomes rate reached 84.06%. (Table 4). The 89 surgical patients were followed-up for more than 1 year. JOA score improved significantly in 82 patients, but nerve root entrapment syndrome occurred in 3 cases, adjacent segment disease occurred in 2 cases.

Resorption of Giant Lumbar Disc Herniation

For convenience in the clinical observation and statistical analysis, we defined resorption rate (RR) \geq 50% as obvious resorption, RR between 30% and 50% as partial resorption, and RR < 30% as no resorption. In the 320 patients treated conservatively, 189 patients (59.06%) experienced obvious or partial resorption. Because the time of the repeat MRI was not fixed, the shortest time interval for resorption was 1 month, and the longest was 8 years. Among the 320 patients, 77 experienced resorption within 6 months, 51 experienced resorption within 6-12 months, and 61 experienced resorption after 12 months. Table 5 shows the classification of each observation index.

Komori type represents the degree of free nucleus pulposus, and the higher the type, the greater the degree of dissociation. In this study, there were 60/235 (25.53%) cases of Komori type 3 obvious absorption, 21/174 (12.07%) cases of type 2, and 0 cases of type 1. A chi-square test showed P < 0.05, and the difference was statistically significant, indicating that the greater the degree of detachment of the protrusion, the more likely it was to resorb. The bull's eye sign on enhanced MRI represents inflammatory responses around the protrusion and neovascularization. In our data, the number of cases with the bull's eye sign and obvious resorption was 37/87 (42.53%), and the difference was statistically significant compared with patients with this sign and no resorption (P < 0.01), suggesting that protrusions create an inflammatory reaction and involve new blood vessel ingrowth. The bull's eye sign was thus more likely to be associated with obvious resorption. Comparison according to the course of disease, significant resorption occurred in 72/269 cases (26.77%) and in 9/140 cases (6.43%) over 1 year. The

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Table 2. Patients' clinical characteristics of gender,
intervertebral disc herniation segment, and first MRI
examination protrusion percentage.

	Category	Case	Percentage	Total number	
Gender	Male	245	59.9%	409	
Gender	Female	164	40.1%	409	
	L2/3	4	1.0%	409	
Disc Herniation	L3/4	16	3.9%		
(levels)	L4/5	164	40.1%		
	L5/S1	225	55.0%		
Direct also also has	MRI scan	279	68.2%		
First check by MRI	Enhanced MRI	130	31.8%	409	

Table 3. The range and mean values for patients' age, course of disease, follow-up, and MRI re-evaluation.

	Interval	Mean ± SD			
Age	14-70 years old	33.18 ± 15.12 years old			
Course of disease	1day- 10years	13.85 ± 25.46 months			
Follow up	1-12 years	3.56 ± 2.81 years			
MRI reinspection	0-8 times	1.94 ± 2.98 times			

chi-square test showed P < 0.01 when comparing, indicating that shorter disease courses were more likely to be associated with resorption.

DISCUSSION

Resorption of Giant Lumbar Disc Herniation

In this study, 189 patients (59.06%) experienced resorption among the 320 patients in the non-surgical treatment group. Conservative treatments constituted absolute bed rest, taking the Xiaosui Huahe decoction, oral celecoxib, and acupuncture. The main functions of the treatments are as follows: The Xiaosui Huahe decoction used in our research can promote nucleus pulposus resorption and relieve nerve root edema, which has been reported in basic trials and clinical studies (18,22). Acupuncture can relieve the high-tension state of the nerve and the symptoms of sciatica (23). In the acute phase, we used celecoxib or acupuncture to relieve pain symptoms. However, celecoxib alone or acupuncture alone can relieve pain, but neither treatment nor bed rest alone has been reported to accelerate resorption. If conservative treatment is chosen for giant disc herniation, clinicians may worry about irreversible complications, such as cauda equina nerve injury, but our clinical study and other related studies

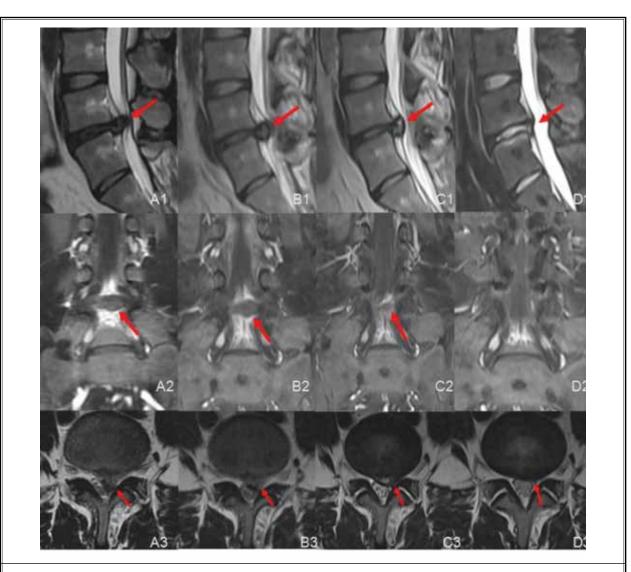


Fig. 4. Enhanced MRI from a 25-year-old woman with lower back pain and radiating pain in her left lower extremity for 2 days due to heavy lifting. Physical examination revealed lumbar physiological radian, L4/L5 tenderness (+) on the left side of the spine, radiating pain to the left leg, straight-leg raise of 50° on the left and 90° on the right, normal bilateral lower limb muscle strength, normal bilateral lower limb skin sensation, no elicitable pathological reflex, and a JOA score of 16 points. Enhanced MRI on May 3, 2018, revealed that the L4/L5 intervertebral disc was protruded, posterior disc surrounding ring reinforcement was seen, bull's-eye sign was present, edge thickness was approximately 1.0 mm, and high-signal protrusion was evident (4A). The diagnosis of lumbar disc herniation was clear, and the patient underwent conservative treatment. This was a case of acute onset of a large lumbar disc herniation, with no significant changes in the herniated disc after 3 months (4B), but with symptom relief and a JOA score of 20. Partial resorption of the protrusion occurred 6 months later (4C), with a JOA score of 22, while complete disappearance of the protrusion occurred 1 year later (4D) when the JOA score was 28.

have reported that this approach is safe. Hong et al (10) reported clinical trial data and showed that patients with LDH had similar long-term outcomes with surgery or conservative treatment, and that patients had little risk of catastrophic exacerbations (cauda equina syndrome or muscle loss) with nonsurgical treatment. A

7-year follow-up study also demonstrated the safety of conservative treatment for giant LDH (19).

Time Analysis of Lumbar Disc Herniation Resorption

Regarding the time to spontaneous absorption

		JOA score [mean ± s.d.]	Improvement	Protrusion	Treat	Excellent and			
	n		rate(%)	percentage (%)	Excellent	Good	Fair	Poor	good rate (%)
Before treatment	320	10.22 ± 3.84	-	70.08 ± 30.95	-	-	-	-	-
After treatment	320	24.88 ± 5.69	74.34 ± 18.92	31.67 ± 24.42	165	104	51	0	84.06

Table 4. JOA score, protrusion percentage, treatment effect, and rate of good and excellent outcomes in the 320 patients who underwent conservative treatment.

Table 5. The number of cases of resorption occurring in each observation index.

Observation ind	ex	Cases	$\begin{array}{c} \textbf{Obvious resorption} \\ \textbf{RR} \geq \textbf{50\%} \end{array}$	Partial resorption $30\% \le RR < 50\%$	No resorption RR < 30%	Operation
Total number		409	81	108	131	89
	Type 1	0	0	0	0	0
Komori types	Type 2	174	21	36	78	39
	Type 3	235	60*	72	53	50
De ll'a sera ai en A	positive	87	37*	26	6	18
Bull's eye sign [△]	negative	43	0	9	26	8
Course of	Within 1 year	269	72*	88	71	38
disease	Over 1 year	140	9	20	60	51

 $^{\circ}$ A total of 130 patients underwent enhanced MRI at the time of initial treatment. *By chi-square test, *P* < 0.05, with the difference being statistically significant.

after disc herniation, according to relevant reports, it is currently believed that absorption usually occurs within 1 year (6). Takada et al (24) found that spontaneous absorption of giant disc herniation occurred earlier than with other types of herniation, at an average of 9 months. Macki et al (12) evaluated 53 cases of largetype LDHs that spontaneously absorbed, and found that clinical symptoms improved (including back pain and lower limb muscle and skin sensation) in 1.33 \pm 1.34 months, and MRI showed spontaneous shrinkage or disappearance of the herniated nucleus pulposus in 9.27 ± 13.32 months. The study concluded that most patients with large LDHs can first undergo non-surgical treatment, and the authors devised the corresponding indications for conservative treatment. Ramos et al (25) conducted a follow-up observation of 72 patients who were clearly diagnosed with LDH on computed tomography scans and who underwent enhanced MRI examination every 6 months. The authors found that 59% of the disc herniation symptoms were relieved, while the nucleus pulposus tissue of the intervertebral disc disappeared within 1 year. In the first 8 months, 66% of the patients had lost the nucleus pulposus tissue, and 83% of the patients developed a ruptured LDH. Kim et al (26) reported the findings for 3 patients who underwent conservative treatment and who experienced spontaneous absorption (2 cases of L2/3 and one

case of L3/4 giant lumbar disc rupture type) and cauda equina nerve symptoms with no serious outcomes after conservative treatment (absolute bed rest, oral drugs, and functional exercise). For the former case, MRI review 2 years later showed that most of the prominent nucleus pulposus tissue had absorbed. For the latter case, the free nucleus pulposus tissue was completely absorbed by the protrusion after 2 months of conservative treatment. Orief et al (14) analyzed 128 inpatients with cervical and LDH, and found that 6 patients obtained relief of root symptoms, such as low back pain, after conservative treatment for 3-6 weeks. Follow-up observation by MRI showed that spontaneous disc absorption occurred 4-9 months after pain relief therapy, and that these patients refused surgical treatment and received oral anti-inflammatory drugs, pain relievers, and physical therapy. After 3-6 weeks of conservative treatment, the patients' pain symptoms were relieved, and after 6-9 months, the pain symptoms had essentially disappeared; MRI showed partial or complete absorption of the herniated nucleus pulposus. Orief et al also found that disc herniation through the posterior longitudinal ligament, which is a large type of nucleus pulposus herniation, is more prone to resorption. Cribb et al (27) reported that non-surgical treatment of large LDHs commonly resulted in volume reduction, and most herniations decreased to 1/3 of the original

size within 6 months. Panagopoulos et al (28) showed in a review, that for patients with lumbar disc protrusion, MRI review within 1 year (7 papers) indicated that 15%–93% of disc herniations shrank or disappeared. In patients with nerve root compression, MRI results (2 papers) were reviewed within 1 year, and 17%–91% of disc herniations shrank or disappeared.

Possible Mechanisms of Spontaneous Absorption After Disc Herniation

The mechanism of resorption after disc herniation may be as follows: 1) Grang et al (29) found that 57% of large and free herniated tissues had capillary infiltration, which was much higher than with other types of herniated disc tissues. In addition, vascular endothelial growth factor, an important vascular growth stimulator, can induce the growth of new capillaries from the edge of the intervertebral disc and promote resorption. 2) Yoshida et al (30) found that tumor necrosis factor α can stimulate cytokine secretion and promote macrophage aggregation, and has strong phagocytic activity and releases a large amount of interleukin, which leads to absorption of the herniated disc tissue. 3) Intervertebral disc tissue is surrounded by the annulus fibrosus and the cartilage endplate, which is the largest nonblood transport tissue in the human body. This tissue is isolated from the human immune system and has antigenicity. When the intervertebral disc tissue breaks through the annulus, an autoimmune reaction occurs to remove the foreign body in the nucleus pulposus. In this process, apoptosis-related factor ligands play an important role by inducing apoptosis and mediating inflammation. Kobayashi et al (31) observed the intervertebral disc herniation tissues of 73 patients undergoing disc herniation surgery, under light microscopy and electron microscopy, and found that new microvessels entering the epidural space grew around the intervertebral disc tissue, and there was a local inflammatory reaction and heavy macrophage infiltration.

The Clinical Predictive Significance of the Enhanced MRI Bull's Eye Sign

The bull's eye sign refers to the circumferential ring enhancement of the herniated disc tissues on enhanced MRI, and it is generally believed that the main cause of this phenomenon is the growth of new blood vessels into herniated tissues (32,33). Autio et al (34) found that the phenomenon of high circular signals, namely the bull's eye sign, could occur around the protruding tissues with annulus rupture, and that the thickness of circular signals was related to the incidence of resorption: resorption was more likely with greater thicknesses. Therefore, it is generally believed that the appearance of the bull's eye sign is of positive significance regarding resorption. In addition, there are also many clinical cases of the bull's eye sign on enhanced MRI, and resorption after conservative treatment has been reported (35). Kawaji et al (36) evaluated 65 patients where enhanced MRI displayed the bull's eye sign and a large lumbar disc prolapse. Twenty-one patients underwent conservative treatment, and 44 underwent surgical treatment. Conservative treatment was undertaken for patients at symptom onset, and enhanced MRI showed that the peripheral volume + 208 cm was reduced from 0.488 to 0.214 ± 181 cm after surgery. As a result, the authors believed that enhanced MRI was effective for predicting lumbar disc absorption. Rajasekarans et al (37) analyzed 118 patients with LDH and found that rupture of the endplate junction (65%) was more common than annulus fibrosus injury (35%). Granulation tissue and blood vessels around the LDH are the main indicators to determine whether the LDH has reabsorbed. The generation and range of vascularization are closely related to the degree of reduction of herniated tissue, degree of absorption, and prognosis (38). Enhanced MRI may be a noninvasive clinical indicator of large lumbar intervertebral disk protrusion and plays an important role in the prognosis of patients with free-type lumbar intervertebral disc protrusions. For patients with significant improvement around protrusions, marked organization of the nucleus pulposus rather than the fiber ring, to some extent, can predict the probability of marked absorption, and may also predict being able to avoid surgery and continue conservative treatment.

CONCLUSION

Patients with giant LDH are less likely to develop progressive nerve injury and cauda equina syndrome if their clinical symptoms improve after treatment. As long as there is no progressive nerve injury or cauda equina syndrome, conservative treatment is preferred for giant disc herniation. Resorption is more likely with higher protrusion percentages of disc herniation in the spinal canal. A ring enhancement around a protruding disc on enhanced MRI (bull's eye sign) is an important indicator of easy resorption. Our study was limited because all patients originated from the same site, and because there was a lack of multicenter randomized controlled trials with which to compare data. This study is also limited because it was a follow-up study and not a randomized control double-blind, and the design is not rigorous. These deficiencies will be addressed in future studies.

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