Massive lumbar disc herniation with complete dural sac stenosis

Chang-Hoon Jeon, Nam-Su Chung, Kwang-Hyun Son, Hyo-Sung Lee

Abstract

Background: Large lumbar disc herniation (LDH) has been reported to have a greater tendency to resolve in clinical and pathomorphological evolutions. However, various definitions of large LDH have been used without validation, and the clinical symptoms of large LDH have not been fully elucidated. We conducted a retrospective analysis to determine the clinical characteristics and treatment outcome of massive LDH with complete dural sac stenosis

Materials and Methods: We retrospectively reviewed 33 cases of LDH with complete dural sac stenosis on magnetic resonance imaging. Complete dural sac stenosis was defined as no recognizable rootlet and cerebrospinal fluid signal on T2-weighed axial MR images. The clinical outcome parameters included back pain, leg pain, Oswestry disability index (ODI), and neurological dysfunction. The paired *t*-test and Wilcoxon's signed rank test were used to compare serial changes in back pain, leg pain and neurological dysfunction.

Results: Mean duration of followup was 66 months (range 24 - 108 months). There were 24 male and 9 female. The mean age was 37 years (range 20 - 53 years). At presentation, mean visual analogue scales for back pain and leg pain were 75.3 ± 19.1 (range 12 - 100) and 80.2 ± 14.6 (range 0 -100), respectively. Mean ODI was 67.1 ± 18.8 (range 26 - 88). Neurological dysfunction was found in 9 patients (27.3%), and the bowel/bladder dysfunction was found in 2 patients (3.1%). Conservative treatment was performed in 21 patients (63.6%) with satisfactory results. Seven patients underwent decompressive surgery, and 5 underwent posterolateral fusion.

Conclusions: A massive LDH with complete dural sac stenosis was found to be associated with severe back and leg pain at presentation, however surgical treatment can be deferred unless significant neurological symptoms occur.

Key words: Intervertebral disc, lumbar, massive disc herniation, MRI

Introduction

The majority of patients with lumbar disc herniation (LDH) show a favorable prognosis with nonoperative treatment.[1-4] Herniated discal tissue spontaneously decreases in size and even disappears.[5-7] The clinical symptoms usually improve regardless of the resolution of herniated discal tissues.[2,8] Large LDH has been reported to have a greater tendency to resolve in clinical and pathomorphological evolutions.[7,9-13] The 'massive' LDH, which was defined in previous studies as the disc material occupying >50% of the spinal canal on axial magnetic resonance (MR) images, showed a successful outcome with nonoperative treatment.[14,15] Therefore, operative treatment of massive LDH can be deferred unless significant neurological symptoms are observed.

On the other hand, the severe dural sac compression by a massive LDH often worries clinicians and patients, and pushes them towards operative treatment for fear of cauda equina syndrome (CES) or significant neurological dysfunction.[2,16-18] Discectomy along with spinal fusion rather than discectomy alone is sometimes preferred for a massive LDH.[19,20]

In the present study, we defined a massive LDH through observations of dural sac morphology rather than by quantifying or qualifying the size of herniated discal tissue. Little information is available in the literature regarding the clinical outcome of extremely large LDH with severe dural sac compression. The aim of this study was to present the

Department of Orthopaedic Surgery, Ajou University School of Medicine, Suwon, Republic of Korea, South Korea

Address for correspondence: Prof. Nam-Su Chung,
San 5, Wonchon-dong, Youngtong-gu, Suwon, Kyounggi-do, South Korea.
E-mail: namsuchung@gmail.com

clinical manifestations and treatment outcomes of massive LDH with complete dural sac stenosis.

Materials and Methods

882 patients were registered in the clinical LDH database at the department of orthopaedic surgery in a tertiary hospital between July 2002 and November 2009. Our LDH database involved the patients' demographics, radiological findings, treatment methods, and clinical assessment at each time of followup. Of these, 38 patients were recognized to have a massive LDH with complete dural sac stenosis, and were included in this study. Complete dural sac stenosis was identified by reviewing dural sac morphologies on lumbar MR images; an LDH with no recognizable rootlet and cerebrospinal fluid signal on T2-weighed axial MR images of the lumbar spine [Figure 1]. Complete dural sac stenosis with ligament flavum hypertrophy and spondylolisthesis were excluded. MR interpretations for inclusion were carried out by three experienced orthopaedic surgeons not involved in the care of the study subjects. Disagreements between interpretations were resolved through discussion and a

Figure 1: T2WI mid sagittal and axial cuts showing (a-c) Massive LDH with complete duralsac stenosis was defined as no recognizable rootlet and cerebrospinal fluid signal on T2-weighed axial MR images of the lumbar spine

consensus opinion was reached. Five of the 38 patients were lost to followup before 2 years had elapsed. Accordingly, 33 patients with a > 2-year followup comprised the study cohort.

Information on gender, age, body mass index (BMI), smoking, occupation, prodromal symptoms, neurological function, treatment, and clinical outcome were obtained from medical records. The clinical outcome parameters included back pain, leg pain, Oswestry disability index (ODI), and neurological dysfunction. Pain was scored using a visual analogue scale (VAS) on a 100 mm horizontal line, where 0 represented no pain and 100 represented the maximum imaginable pain. ODI was scored from 0 to 100, where lower scores indicated less severe symptoms. Neurological dysfunctions were categorized into 5 groups as previously described[21] with modification as follows. 1) Normal: Neurologically intact. 2) Mild: Any sensory change and motor weakness of Medical Research Council (MRC) grade ≥ 4 in any lower extremity muscle by the manual muscle testing.[22] 3) Moderate: Any sensory change and motor weakness of MRC grade < 4 in any lower extremity muscle. 4) Incomplete or impending CES: Signs of saddle sensory disturbance, bilateral sciatica, and lower extremity weakness, but intact bowel/bladder function. 5) Complete CES: Any other sign of CES with uncontrolled bowel/bladder function. Outcome parameters were measured at baseline, 1 month, 6 months, 12 months, and at last followup.

Patients with impending or established CES, progressive neurological dysfunction, or intractable pain were treated surgically. Standard surgical procedures involved the removal of herniated tissue and wide neural decompression. Spinal fusion was additionally performed in cases with pre-existing degeneration or instability. All surgeries were performed by the senior author (C.H.J).

Descriptive statistics are summarized as frequencies and percentages for categorical variables, and as means and standard deviations for continuous variables. The paired *t*-test and Wilcoxon's signed rank test were used to compare serial changes in back pain, leg pain and neurological dysfunction. Interobserver reliability for the interpretation of complete dural sac stenosis was assessed using kappa values, which were interpreted as follows: Moderate (0.41 ≤ κ <0.60), substantial (0.60 ≤ κ <0.80), and almost perfect (0.80 ≤ κ <1.00).[23] Statistical analysis was carried out using SPSS version 14.0 software (SPSS Inc, Chicago, IL). A *P* value of <0.05 was considered significant.

Results

Of the 33 massive LDHs with complete dural sac stenosis,

26 were identified as extrusions, and the remaining 7 were sequestrations. The mean age of the 24 male and 9 female patients was 37 years (range 20-53 years), and the mean BMI was 24.2 m/kg² (range 19.0-33.7 m/kg²). Eighteen patients (55%) were office workers, and 3 (9%) were engaged in heavy labor. Eleven patients (33%) were smokers. One patient had a herniated disc at L2-3, three at L3-4, nineteen at L4-5, and 10 at L5-S1. The mean duration of followup was 66 months (range 24-108 months).

Twenty nine patients (87.9%) had prodromal back or leg pain with a mean VAS score of 36.4 ± 32.1 (range 0-71) for 26.1 ± 32.2 days (range 3-90 days) before presentation. At presentation, mean VAS scores for back pain and leg pain were 75.3 ± 19.1 (range 12-100) and 80.2 ± 14.6 (range 0-100), respectively. Back and leg pain were aggravated at 4.2 (range 0-15 days) and 3.3 (range 0-7 days) days before presentation, respectively. The mean ODI score was 67.1 ± 18.8 (range 26-88). Neurological symptoms occurred for a mean 3.1 days (range 0-60 days) before presentation. Twenty four patients (72.7%) had normal or mild neurological dysfunction. Nine patients (27.3%) had neurological dysfunction. Three patients (9%) showed moderate dysfunction. Bowel and bladder symptoms were present in 2 patients (6.1%) [Table 1].

Twenty one patients (63.6%) were treated nonoperatively. Nonoperative treatment included oral medication, physical therapy, and patient education. Commonly used medications were nonsteroidal antiinflammatory drugs, corticosteroids, muscle relaxants, and opioid pain medications. Epidural block was performed in 19 patients. Three patients (9%) underwent decompression and primary

posterolateral fusion for concomitant degenerative changes. Both back pain and leg pain decreased significantly within 1 month, and continued to decrease at the time of last followup. The mean VAS score for back pain was 75.3 ± 19.1 at presentation and 35.3 ± 16.4 at last followup ($P < 0.001$) [Figure 2]. The mean VAS score for leg pain was 80.2 ± 14.6 at presentation and 24.9 ± 19.9 at last followup ($P < 0.001$) [Figure 3]. ODI decreased significantly within 6 months [Figure 4]. The mean ODI was 67.1
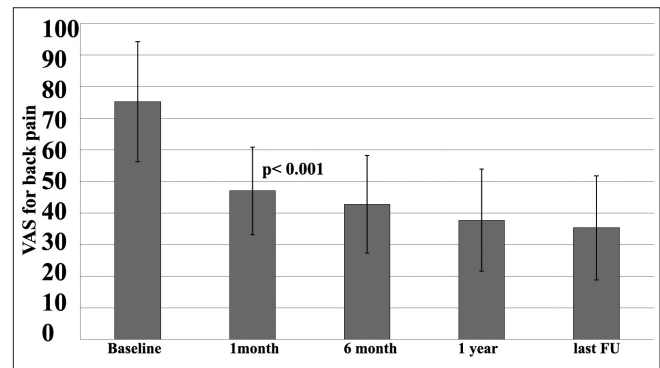
Figure 2: Bar diagram showing mean VAS for back pain during the followup period. Back pain significantly decreased within one month ($P < 0.001$) and continued to decrease at last followup
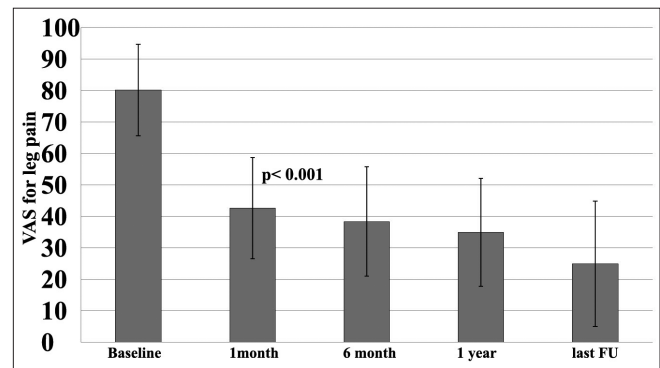
Figure 3: Bar diagram showing mean VAS for leg pain during the followup period. Leg pain significantly decreased within one month ($P < 0.001$) and continued to decrease at last followup
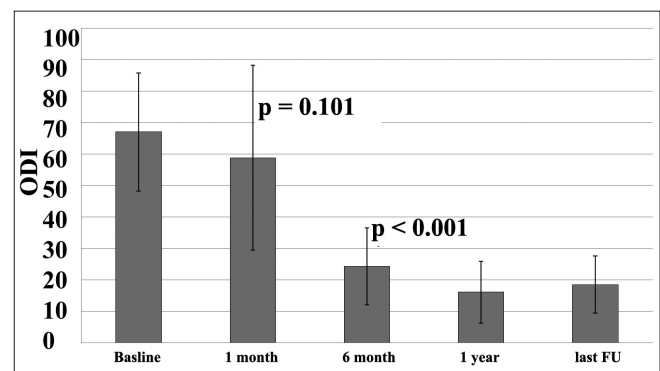
Figure 4: Bar diagram showing mean ODI score during the followup period. ODI score significantly decreased within 6 month ($P < 0.001$) and continued to decrease at last followup

Table 1: Clinical presentation

Symptoms and signs	Average (range)
Prodromal back or leg pain	
Duration (days)	26.1 (3 to 90)
Severity (VAS)	36.4±32.1 (0 to 71)
Back pain at presentation	
Aggravation (days)	4.2 (0 to 15)
Severity (VAS)	75.3±19.1 (12 to 100)
Leg pain at presentation	
Aggravation (days)	3.3 (0 to 7)
Severity (VAS)	80.2±14.6 (0 to 100)
Oswestry disability index	67.1±18.8 (26 to 88)
Neurological dysfunction	
Duration (days)	3.1 (0 to 60)
Severity	
Normal	19 (57.6%)
Mild	5 (15.2%)
Moderate	3 (9%)
Incomplete CES	4 (12.1%)
Complete CES	2 (6.1%)

VAS = Visual analogue scale, CES = Cauda equina syndrome

± 18.8 at presentation and 18.5 ± 9.1 at last followup ($P < 0.001$). Neurological function also improved significantly within 1 month and continued to improve at last followup ($P = 0.015$) [Figure 5].

Three patients (9.1%) underwent discectomy along with posterolateral fusion and 9 patients (27.3%) underwent discectomy. Two of the 9 discectomy patients underwent revision surgery with posterolateral fusion for persistent symptoms. Back pain, leg pain, and disability decreased within 1 month. The mean VAS score for back pain was 68.5 ± 23.4 at presentation and 21.5 ± 22.8 at 1 month ($P < 0.001$). The mean VAS score for leg pain was 88.7 ± 19.1 at presentation and 19.3 ± 28.6 at 1 month ($P < 0.001$). The mean ODI was 78.8 ± 25.4 at presentation and 14.6 ± 10.9 at last followup ($P < 0.001$).

At the last followup, 26 of the 33 patients (78.8%) had normal neurological function. Two patients that had underwent operative treatment showed persistent bladder dysfunction only.

The kappa value of interobserver agreement regarding the interpretation of complete dural sac stenosis was 0.78, which indicated substantial agreement.

DISCUSSION

Many efforts have been made to derive a nomenclature and classification for LDH that accurately describes the morphologies of displaced discal tissues.[24-30] LDH sizes are measured quantitatively by computing greatest cross-sectional areas on axial computed tomographic or MR images.[31,32] The joint society committee of North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology proposed a qualitative grading scheme based on the following definitions; mild (canal compromise of less than one third of the canal), moderate (between one third and two thirds), or severe
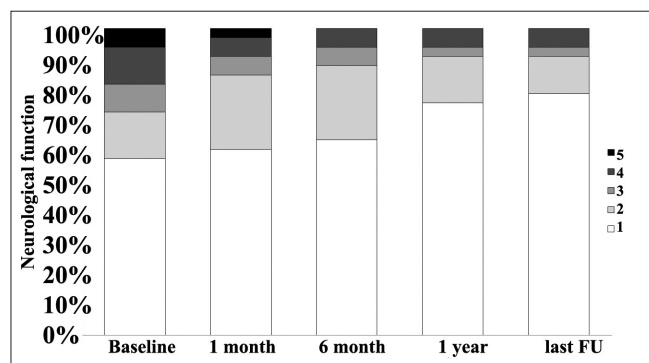
Figure 5: Bar diagram showing neurological function significantly improved within one month ($P = 0.015$) and continued to improve at last followup

(over two thirds).[29] However, quantification or estimation of LDH size is rarely performed because these are based on one slice of an LDH and cannot provide information about the clinical significance of lesions.[31] *Schizas et al.*,[33] proposed a qualitative grading system for lumbar spinal stenosis based on dural sac morphology rather than dural cross-sectional area; this system was found to be more reliable and valid for the assessment of a patient's symptoms, and more reliable from the perspective of clinician decision-making.[34] *Pfirrmann et al.*,[30] graded LDHs based on nerve root morphology; this system was reliable and consistent with surgical findings. *Beattie et al.*,[28] reported a strong association between deformation of the dural sac and symptoms in LDH patients. For similar reasons, we defined a massive LDH based on observations of the dural sac morphology rather than quantifying or estimating the size of herniation.

The present study involved 33 patients with massive LDH with complete dural sac stenosis among 882 patients in our LDH database (3.7%). The reliability of assessments based on dural sac morphology is reportedly moderate to substantial.[32,33] In this study, the reliability of dural sac morphology was found to be substantial (kappa value was 0.78).

The typical presenting symptom of LDH is acute or chronic intermittent lower back pain with associated leg pain. It is widely accepted that both of these pains resolve faster and more consistently when LDHs are large.[7,10,11,13,35] However, the relationship between LDH size and clinical symptom severity has not been fully elucidated.[28] In this study, the mean VAS scores of back and leg pain at presentation were 75.3 ± 19.1 and 80.2 ± 14.6, respectively, which are higher than those previously reported values of general LDH.[35-39] This difference suggests that massive LDHs with complete dural sac stenosis cause more severe back pain and leg pain at presentation, which is probably because larger LDHs produce higher levels of proinflammatory mediators and cytokines.[40] Neurological dysfunction was observed in 42.4% ($n = 14$) of our study subjects. However, bowel/bladder symptoms appeared in only 2 patients (6.1%). Furthermore, our results demonstrate that neurological function was not severely affected by complete obliteration of the dural sac, which is consistent with previous reports on massive LDH.[14,15] These findings indicate that operative treatment can be deferred for patients with massive LDH with complete dural sac stenosis, unless significant neurological symptoms are observed.

Cribb *et al.*,[14] reported 15 massive LDH patients (disc material occupying >50% of the spinal canal) with nonoperative treatment. Repeat MR scanning after a mean 2 years showed a resolution of the herniation

in 14 patients. No CES was developed in their series. Benson *et al*.,[15] reported 37 patients with conservatively treated massive LDH (disc material occupying >50% of the spinal canal). Eighty-three percent had a complete and sustained recovery after 2-year followup. Only four patients required a discectomy. The average Oswestry disability index improved from 58% to 15%. In this study, conservative treatment yielded a significant improvement in 63.6% of the study population. In particular, back and leg pain significantly improved within 1 month. Neurological deterioration was not observed in any patient.

Several limitations of this study warrant consideration. The first concerns its retrospective nature. Data associated with the use of medical records, miscoding, and a lack of clinical information can adversely affect results. The second limitation is that we did not compare the demographics, clinical characteristics, and followup results in our cohort with a moderately sized LDH. For this reason, we were unable to determine the clinical characteristics and the effects of nonoperative treatments. Moreover, other radiological parameters such as LDH size, canal area, modic changes, ligament flavum hypertrophy, facet arthritis, and dynamic instability were not analyzed. Additional studies regarding the clinical relevance, treatment outcomes, and subgroup analysis are warranted.

To conclude, although a massive LDH with complete dural sac stenosis is initially associated with severe back and leg pain, nonsurgical treatment yields a favorable outcome. Surgical treatment can be deferred unless significant neurological symptoms occur.

REFERENCES

1. Saal JA, Saal JS. Nonoperative treatment of herniated lumbar intervertebral disc with radiculopathy. An outcome study. Spine (Phila Pa 1976) 1989;14:431-7.
2. Postacchini F. Management of herniation of the lumbar disc. J Bone Joint Surg Br 1999;81:567-76.
3. Benoist M. The natural history of lumbar disc herniation and radiculopathy. Joint Bone Spine 2002;69:155-60.
4. Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse: Updated Cochrane Review. Spine (Phila Pa 1976) 2007;32:1735-47.
5. Teplick JG, Haskin ME. Spontaneous regression of herniated nucleus pulposus. AJR Am J Roentgenol 1985;145:371-5.
6. Ito T, Yamada M, Ikuta F, Fukuda T, Hoshi SI, Kawaji Y, *et al*. Histologic evidence of absorption of sequestration-type herniated disc. Spine (Phila Pa 1976) 1996;21:230-4.
7. Jensen TS, Albert HB, Soerensen JS, Manniche C, Leboeuf-Yde C. Natural course of disc morphology in patients with sciatica: An MRI study using a standardized qualitative classification system. Spine (Phila Pa 1976) 2006;31:1605-12;discussion 1613.
8. Rhee JM, Schaufele M, Abdu WA. Radiculopathy and the herniated lumbar disc. Controversies regarding pathophysiology
9. Bozzao A, Gallucci M, Masciocchi C, Aprile I, Barile A, Passariello R. Lumbar disk herniation: MR imaging assessment of natural history in patients treated without surgery. Radiology 1992;185:135-41.
10. Komori H, Shinomiya K, Nakai O, Yamaura I, Takeda S, Furuya K. The natural history of herniated nucleus pulposus with radiculopathy. Spine (Phila Pa 1976) 1996;21:225-9.
11. Saal JA, Saal JS, Herzog RJ. The natural history of lumbar intervertebral disc extrusions treated nonoperatively. Spine (Phila Pa 1976) 1990;15:683-6.
12. Matsubara Y, Kato F, Mimatsu K, Kajino G, Nakamura S, Nitta H. Serial changes on MRI in lumbar disc herniations treated conservatively. Neuroradiology 1995;37:378-83.
13. Ahn SH, Ahn MW, Byun WM. Effect of the transligamentous extension of lumbar disc herniations on their regression and the clinical outcome of sciatica. Spine (Phila Pa 1976) 2000;25:475-80.
14. Cribb GL, Jaffray DC, Cassar-Pullicino VN. Observations on the natural history of massive lumbar disc herniation. J Bone Joint Surg Br 2007;89:782-4.
15. Benson RT, Tavares SP, Robertson SC, Sharp R, Marshall RW. Conservatively treated massive prolapsed discs: A 7-year followup. Ann R Coll Surg Engl 2010;92:147-53.
16. Shapiro S. Cauda equina syndrome secondary to lumbar disc herniation. Neurosurgery 1993;32:743-6; discussion 746-7.
17. Ahn UM, Ahn NU, Buchowski JM, Garrett ES, Sieber AN, Kostuik JP. Cauda equina syndrome secondary to lumbar disc herniation: a meta-analysis of surgical outcomes. Spine (Phila Pa 1976) 2000;25:1515-22.
18. Louison R, Barber JB. Massive herniation of lumbar discs with compression of the cauda equina--a surgical emergency; report of two cases. J Natl Med Assoc 1968;60:188-90.
19. Postacchini F. Results of surgery compared with conservative management for lumbar disc herniations. Spine (Phila Pa 1976) 1996;21:1383-7.
20. Satoh I, Yonenobu K, Hosono N, Ohwada T, Fuji T, Yoshikawa H. Indication of posterior lumbar interbody fusion for lumbar disc herniation. J Spinal Disord Tech 2006;19:104-8.
21. Shi J, Jia L, Yuan W, Shi G, Ma B, Wang B, *et al*. Clinical classification of cauda equina syndrome for proper treatment. Acta Orthop 2010;81:391-5.
22. Rahimi-Movaghar V, Saadat S, Vaccaro AR, Ghodsi SM, Samadian M, Sheykhmozaffari A, *et al*. The efficacy of surgical decompression before 24 hours versus 24 to 72 hours in patients with spinal cord injury from T1 to L1--with specific consideration on ethics: A randomized controlled trial. Trials 2009;10:77.
23. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159-74.
24. Milette PC, Melancon D, Dupuis PR, Vadeboncoeur R, Bertrand G, Pelletier JP, *et al*. A simplified terminology for abnormalities of the lumbar disk. Can Assoc Radiol J 1991;42:319-25.
25. Kim KY, Kim YT, Lee CS, Shin MJ. MRI classification of lumbar herniated intervertebral disc. Orthopedics 1992;15:493-7.
26. Brant-Zawadzki M, Jensen M. Spinal nomenclature. Spine (Phila Pa 1976) 1995;20:388-90.
27. Wiltse LL, Berger PE, McCulloch JA. A system for reporting the size and location of lesions in the spine. Spine (Phila Pa 1976) 1997;22:1534-7.
28. Beattie PF, Meyers SP, Stratford P, Millard RW, Hollenberg GM. Associations between patient report of symptoms and

anatomic impairment visible on lumbar magnetic resonance imaging. Spine (Phila Pa 1976) 2000;25:819-28.

29. Fardon DF, Milette PC. Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Nomenclature and classification of lumbar disc pathology. Recommendations of the Combined task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. Spine (Phila Pa 1976) 2001;26:E93-E113.

30. Pfirrmann CW, Dora C, Schmid MR, Zanetti M, Hodler J, Boos N. MR image-based grading of lumbar nerve root compromise due to disk herniation: Reliability study with surgical correlation. Radiology 2004;230:583-8.

31. Milette PC. Classification, diagnostic imaging, and imaging characterization of a lumbar herniated disk. Radiol Clin North Am 2000;38:1267-92.

32. Lurie JD, Tosteson AN, Tosteson TD, Carragee E, Carrino JA, Kaiser J, *et al.* Reliability of magnetic resonance imaging readings for lumbar disc herniation in the Spine Patient Outcomes Research Trial (SPORT). Spine (Phila Pa 1976) 2008;33:991-8.

33. Schizas C, Theumann N, Burn A, Tansey R, Wardlaw D, Smith FW, *et al.* Qualitative grading of severity of lumbar spinal stenosis based on the morphology of the dural sac on magnetic resonance images. Spine (Phila Pa 1976) 2010;35:1919-24.

34. Schizas C, Kulik G. Decision-making in lumbar spinal stenosis: A survey on the influence of the morphology of the dural sac. J Bone Joint Surg Br 2012;94:98-101.

35. Osterman H, Seitsalo S, Karppinen J, Malmivaara A. Effectiveness of microdiscectomy for lumbar disc herniation: A randomized controlled trial with 2 years of followup. Spine (Phila Pa 1976) 2006;31:2409-14.

36. Buttermann GR. Treatment of lumbar disc herniation: Epidural steroid injection compared with discectomy. A prospective, randomized study. J Bone Joint Surg Am 2004;86-A: 670-9.

37. Weinstein JN, Lurie JD, Tosteson TD, Skinner JS, Hanscom B, Tosteson AN, *et al.* Surgical vs nonoperative treatment for lumbar disk herniation: The Spine Patient Outcomes Research Trial (SPORT) observational cohort. JAMA 2006;296:2451-9.

38. Peul WC, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JA, Tans JT, *et al.* Surgery versus prolonged conservative treatment for sciatica. N Engl J Med 2007;356:2245-56.

39. Atlas SJ, Keller RB, Wu YA, Deyo RA, Singer DE. Long term outcomes of surgical and nonsurgical management of sciatica secondary to a lumbar disc herniation: 10 year results from the maine lumbar spine study. Spine (Phila Pa 1976) 2005;30:927-35.

40. Burke JG, Watson RW, McCormack D, Dowling FE, Walsh MG, Fitzpatrick JM. Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. J Bone Joint Surg Br 2002;84:196-201.

Author Help: Reference checking facility

The manuscript system (www.journalonweb.com) allows the authors to check and verify the accuracy and style of references. The tool checks the references with PubMed as per a predefined style. Authors are encouraged to use this facility, before submitting articles to the journal.

- The style as well as bibliographic elements should be 100% accurate, to help get the references verified from the system. Even a single spelling error or addition of issue number/month of publication will lead to an error when verifying the reference.
- Example of a correct style
  Sheahan P, O'leary G, Lee G, Fitzgibbon J. Cystic cervical metastases: Incidence and diagnosis using fine needle aspiration biopsy. Otolaryngol Head Neck Surg 2002;127:294-8.
- Only the references from journals indexed in PubMed will be checked.
- Enter each reference in new line, without a serial number.
- Add up to a maximum of 15 references at a time.
- If the reference is correct for its bibliographic elements and punctuations, it will be shown as CORRECT and a link to the correct article in PubMed will be given.
- If any of the bibliographic elements are missing, incorrect or extra (such as issue number), it will be shown as INCORRECT and link to possible articles in PubMed will be given.