EXTRAFORAMINAL LUMBAR DISK HERNIATIONS LEAD TO NEUROPLASTIC CHANGES: A STUDY USING QUANTITATIVE SENSORY TESTING

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ABSTRACT: *Introduction*: Extraforaminal lumbar disk herniations are characterized by distinct clinical features in comparison to paramedian lumbar disk herniations. *Methods*: We applied the quantitative sensory testing (QST) protocol of the German Research Network on Neuropathic Pain in 63 patients with a single lumbar disk herniation. They were categorized in 2 groups: (I) an intraspinal (group I; $n = 47$, 75%) and an extraforaminal (group E; $n = 16$, 25%). *Results*: The wind-up ratio for assessing endogenous pain-modulating pathways was higher in group E (2.9 ± 2) than in group I (1.4 ± 1; $P = 0.021$). After a subsequent series of pinprick stimuli, an increase in pain assessed by the numeric rating scale could be shown in group E (2.1 ± 2 vs 1.1 ± 1; $P = 0.032$). *Discussion*: Extraforaminal compression is associated with chronic as well as neuropathic pain, presumably caused by direct compression of the dorsal root ganglion, which may preferentially promote specific chronic pain mechanisms.
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A lumbar disk herniation may be a life-changing event for the affected patient. In addition to conservative or surgical treatment as possible therapeutic approaches, pain intensity and recovery may be influenced by several important factors.[1–3] Besides gender[1] and physical activity,[3] the location of the disk herniation may also play a crucial role.[4–6]

Extraforaminal lumbar disk herniations represent 7%–12% of all lumbosacral disk herniations.[6] In comparison to paramedian lumbar disk herniations, increased pain occurs, presumably caused by direct compression of the dorsal root ganglion.[4,5,7] Nevertheless, despite the presence of large retrospective studies, prospective trials on this topic are still lacking. Regardless of generally accepted differing features of extraforaminal lateral disk herniations in comparison to paramedian intraspinal herniations, pain and sensory dysfunction have rarely been investigated.[4–6] Quantitative sensory testing (QST) has become a valuable tool for quantifying sensory function.[8,9] It is a psychophysiologic test of various sensory modalities that permits investigation of preserved sensation and also of subclinical deficits.[8,10]

The purpose of this study was to investigate the influence of the location of the herniated disk (intra- vs. extraforaminal) on pain intensity and sensory function.

METHODS

Subjects. Pain management was not delayed or altered by participation in this study. All subjects gave their informed consent. The study was approved by the local ethics committee of the Medical University Innsbruck (AN5124 327/4.9 357/5.14) in accordance with the ethical principles originating from the Declaration of Helsinki and in compliance with Good Clinical Practice. Consecutive patients were considered for inclusion when either they had a mediolateral intraspinal (paramedian) or an extraforaminal single-level disk herniation confirmed on MRI and subjective sensory dysfunction in the corresponding nerve root distribution from L3 to S1.[11] All patients had an indication for sequestrectomy according to the guidelines of the German Society of Neurosurgery (DGNC) and the German Society of Orthopedics and Orthopedic Surgery (DGOOC). All participants were on best medical pain treatment, but sufficient pain relief was not achieved. None of the included patients had a history of previous back surgery or peripheral nervous system disorders. Participants with metabolic or toxic disorders that can cause neuropathy were excluded.

Questionnaire, Medical History, and Clinical Examination. The evaluation included a detailed medical history, a physical examination, and various questionnaires. The following standardized spine outcome measures were prospectively assessed: (1) The numeric rating scale (NRS) for leg pain on a 0–10 rating scale, with higher scores indicating worse pain.[12] (2) The Beck Depression Inventory (BDI), a multiple choice self-reported inventory for measuring the severity of depression and responsiveness to treatment (outcomes as follows: 0–9 = minimal depression; 10–18 = mild depression; 19–29 = moderate depression; 30–63 = severe depression).[13] (3) Generic health status, assessed with the EuroQoL 5-Dimension (EQ-5D). The EQ-5D-3L consists of the EQ-5D descriptive system and the EQ visual analog scale (EQ-

Additional supporting information may be found in the online version of this article.

Abbreviations: BDI, Beck Depression Inventory; CDT, cold detection threshold; CPT, cold pain threshold; DGNC, German Society of Neurosurgery; DGOOC, German Society of Orthopedics and Orthopedic Surgery; E, extraforaminal; EQ-5D, EuroQoL 5-Dimension; EQ-VAS, EQ Visual Analog Scale; HPT, heat pain threshold; I, intraspinal; MDT, mechanical detectin threhsold; MPS, mechanical pain sensitivity; MPT, mechanical pain threshold; NRS, numeric rating scale; ODI, Oswestry Disability Index; QST, quantitative sensory testing; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio

Key words: extraforaminal lumbar disk herniation, lumbar disk herniation, lumbar radiculopathy, lumbar sequestrectomy, neuropathic pain, quantitative sensory testing

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Table 1. Demographics and clinical characteristics of 63 patients with intraspinal (I) and extraforaminal (E) lumbar disk herniations

	Group I (n = 47)	Group E (n = 16)	P-value
Demographic characteristics			
Age, in years (mean ± SD)	44.1 ± 10	50.6 ± 8	0.020*
Female gender [n (%)]	19 of 47 (40)	2 of 16 (12)	0.042*
BMI (mean ± SD)	26.7 ± 4	27.4 ± 4	0.608
Smoking [n (%)]	23 of 47 (48)	7 of 16 (43)	0.722
Cigarettes per day (mean ± SD)	6.8 ± 8	8 ± 10	0.619
Alcohol none [n (%)]	13 of 47 (27)	3 of 16 (18)	0.395
Daily [n (%)]	0 of 47 (0)	4 of 16 (25)	
Weekly [n (%)]	2 of 47 (4)	1 of 16 (6)	
Incidentally [n (%)]	32 of 47 (68)	8 of 16 (50)	
ASA score [n (%)]			0.161
1	29 of 47 (61)	7 of 16 (43)	
2	18 of 47 (38)	8 of 16 (50)	
3	0 of 47 (0)	1 of 16 (6)	
Nerve root injection with steroid [n (%)]	10 of 47 (21)	6 of 16 (37)	0.201
Pain characteristics			
Leg-raising test positive [n (%)]	37 of 47 (78)	8 of 16 (50)	0.929
Duration of pain, in days (mean ± SD)	175.6 ± 275	62.5 ± 63	0.591
Radicular pain [n (%)]			0.004*
L3	3 of 47 (6)	2 of 16 (12)	
L4	4 of 47 (8)	4 of 16 (25)	
L5	17 of 47 (36)	10 of 16 (62)	
S1	23 of 47 (48)	0 of 16 (0)	

ASA, American Society of Anesthesiology; BMI, body mass index.

**Statistically significant at* $\mathbf{P} < 0.05$.

VAS), and assesses 5 dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. Each dimension has 3 levels: no problems; some problems; and extreme problems. The EQ-VAS is a vertical 20-cm VAS with the endpoints labeled as best imaginable health state at the top and worst imaginable health state at the bottom, with numeric values of 100 and 0, respectively.[14] (4) The Oswestry Disability Index (ODI), a validated, reliable, and widely used tool for the assessment of therapeutic effects. The ODI consists of 10 sections, with 6 questions in each section. A lower score indicates a higher level of function. An overall score for all 10 sections of the ODI is computed and used as the ODI score. The standardized version of the ODI can be computed by rescaling the score to the range 0–100.[15]

Magnetic Resonance Imaging. MRI of the lumbar spine was performed in a standardized fashion on a 3.0-T MRI scanner (Siemens, Verio). The protocols included sagittal T1-TSE and T2-TSE, axial T1-TSE, and PD/T2-TSE. Each MRI was examined for evidence of disk degeneration (Pfirrmann degeneration grade) and degenerative changes of the intervertebral endplates (Modic changes) by an independent neuroradiologist blinded to the clinical signs and symptoms.[16,17] Lumbar disk herniations were further classified as intraspinal or extraforaminal.[11]

Quantitative Sensory Testing. QST was performed by a single investigator. Evaluation was conducted in the dermatome of the affected nerve root that was determined clinically by radicular pain, weakness, and reflex loss, if present, in conjunction with the radiologic findings.

Patients were given clear and identical instructions. The thermal tests were performed using a sensory analyzer (TSA-II; Medoc, Israel). Z-transformation was performed for all QST values to compare the patient's QST data with control data that were independent of different units across all QST values. $Z > 0$ suggested a gain of sensitivity, whereas $Z < 0$ indicated a loss of sensitivity in the tested dermatome compared with controls. To adapt parameters to the available reference values, log transformation was performed. To eliminate zero values for numeric pain ratings, a small constant (+0.01) was added before log transformation. Cold and warm detection thresholds were measured first (CDT, WDT), followed by cold pain and heat pain thresholds (CPT, HPT). The mechanical detection threshold (MDT) was measured using a standardized set of modified von Frey hairs (Somedic, Sweden) that exert forces on bending between 0.25 and 512 mN. The vibration detection threshold (VDT) was obtained with a Rydel–Seifer tuning fork (64 Hz, 8/8 scale). The mechanical pain threshold (MPT) was measured by a custom-made pinprick set with forces from 8 to 512 mN. Mechanical pain sensitivity (MPS) was assessed using the same pinprick stimuli to obtain a stimulus response function for pinprick evoked pain. Subjects were asked to give a pain rating for each stimulus on a 0–10 NRS (0 = "no pain" and 10 = "most intense pain imaginable"). The wind-up ratio (WUR) was acquired by applying a single pinprick stimulus (256 mN) and a subsequent series of 10 pinprick stimuli. The mean pain rating of trains divided by the mean pain rating to single stimulus (MPS) was calculated as WUR. A pressure-gauge device (FDK 20; Wagner Instruments, Greenwich, Connecticut) was used to measure the pressure pain threshold (PPT).[9,18]

Statistical Analysis. All patients with a complete examination were considered for inclusion in the study population. All values were expressed as mean ± SD. The Kolmogorov–Smirnov test was used for testing normal distribution. The unpaired Student's t-test, Mann–Whitney U-test, and Fisher's exact test were used to analyze differences in clinical and demographic characteristics and in clinical outcome variables.

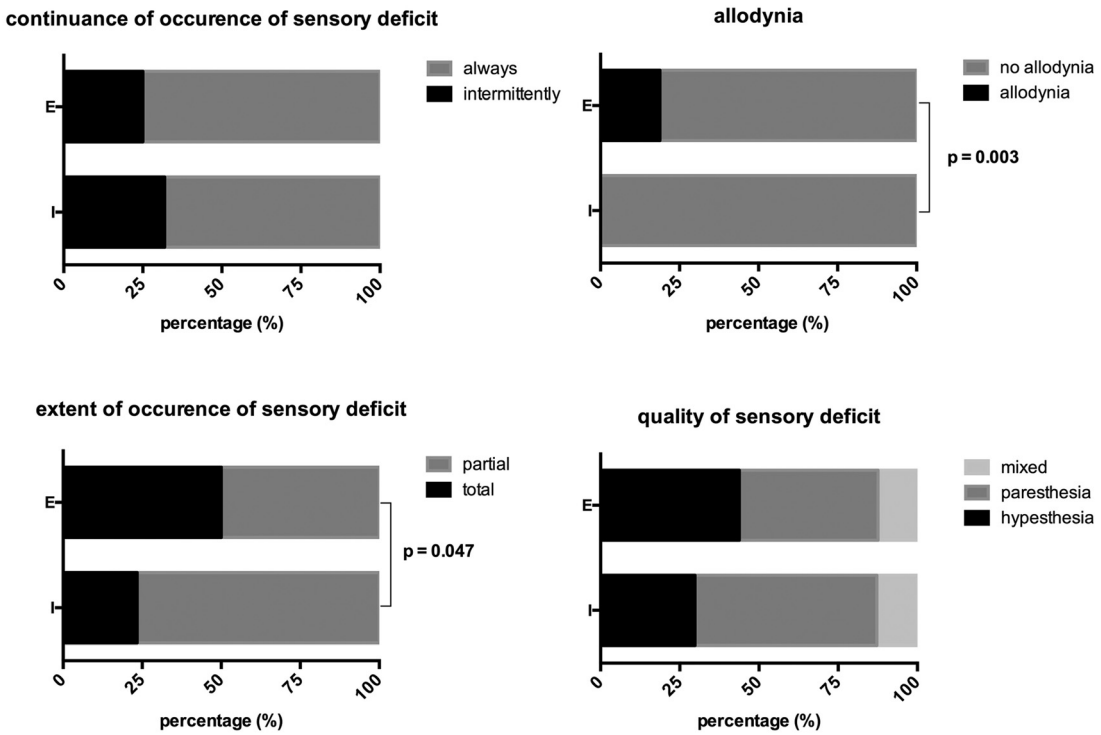

FIGURE 1. Characteristics of sensory dysfunction. I = intraspinal lumbar disk herniation, E = extraforaminal lumbar disk herniation, p = significant difference, total = whole dermatome affected, partial = part of dermatome affected.

$P < 0.05$ was considered statistically significant. All statistical evaluations were performed with SPSS version 21.0 for Windows (IBM SPSS, Armonk, New York). *Z*-transformations were performed using Microsoft Excel for Macintosh version 15.4 (Microsoft Corp., Redmond, Washington). Figures were designed using GraphPad Prism version 5.0 for Mac OS X (GraphPad Software, Inc., La Jolla, California; www.graphpad.com).

RESULTS

Sixty-six patients who met the initial inclusion and exclusion criteria were selected for participation in the study. Two patients withdrew informed consent, and 1 patient had an emergency operation, so that study investigation could not be performed. Therefore, 63 patients were enrolled in the study and were categorized into 2 groups based on the localization of the lumbar disk herniation, which was confirmed by preoperative MRI: intraspinal lumbar disk herniation (group I: $n = 47$, 75%) and extraforaminal lumbar disk herniation (group E: $n = 16$, 25%).

The demographic details and characteristics of the included patients are presented in Table 1. The most commonly affected nerve root was S1 in group I and L5 in group E. Patients in group E were significantly older than those in group I.

The characteristics of sensory dysfunction in each group are shown in Figure 1. Allodynia was only present in group E (18% vs. 0%). Sixty-five percent of those in group I and 82% in group E took analgesics on a regular basis before surgery ($P > 0.05$). No differences were found in reflex or motor deficits (loss of reflexes: 14% [group E] vs. 40% [group I]; motor deficits: 68% [group E] vs. 48% [group I]; $P > 0.05$).

The results of the QST thresholds are presented in Table 2. CDT was found to be significantly different between group I and group E, indicating superior cold detection thresholds in group I. WUR was higher in group E than in group I (Fig. 2).

Leg and back pain on NRS were not different between groups ($P > 0.05$). All patients had radicular pain (100%). ODI indicated significantly higher disability in sleeping in group E ($P = 0.043$). There were no differences in EQ-5D and EQ-5D VAS between groups (see Table S1 in Supplementary Material available online).

The most common Pfirrmann grade was grade IV in both groups and there was no significant difference between groups. Sixty-two percent of those in group I and 63% in group E showed Modic changes on MRI ($P > 0.05$).

DISCUSSION

Allodynia only occurred in patients with an extraforaminal lumbar disk herniation. These patients more frequently have sleep disturbances. WUR was more severe in the group with extraforaminal lumbar disk herniations. Pain rating on NRS, however, showed no differences in leg or back pain between groups.

In agreement with recent literature on clinical characteristics associated with extraforaminal lumbar disk herniations, the patients in our study group were

Table 2. Differences in thermal and mechanical perception thresholds.

QST parameters *Z*-scores	Group I (*n* = 47)	Group E (*n* = 16)	*P*-value
CDT (C)	1.4 ± 1	0.3 ± 1	0.006
WDT (C)	0.9 ± 0.2	0.6 ± 1	0.060
CPT (C)	−0.2 ± 1	−0.2 ± 0.9	0.801
HPT (C)	1.0 ± 2	0.6 ± 1	0.309
MDT (mN)	1.2 ± 1	0.7 ± 0.7	0.229
MPT (mN)	2.6 ± 0.1	1.4 ± 1	0.329
VDT (Hz)	−1.9 ± 3	−1.6 ± 2	0.709
MPS (1–10)	−1.7 ± 2	−0.3 ± 2	0.066
PPT (kg/cm^2)	0.2 ± 1	0.2 ± 1	0.915

QST data are presented as mean ± SD. CDT, cold detection threshold, CPT, cold pain threshold; E, extraforaminal lumbar disk herniation; HPT, heat pain threshold, MDT, mechanical detection threshold, I, intraspinal lumbar disk herniation; MPT, mechanical pain threshold, MPS, mechanical pain sensitivity, QST, quantitative sensory testing; VDT, vibration detection threshold, WDT, warm detection threshold.

significantly older in the extraforaminal group.[4] In contrast to published data, however, female gender was more common in patients with an intraspinal lumbar disk herniation.[4] There were no differences in the prevalence of motor or reflex dysfunction.[4,6]

Previous studies have indicated that extraforaminal disk herniations are frequently related to radiating leg pain.[4–6] In our study population, all patients had medically refractory radicular pain, an indication for sequestrectomy. Leg and back pain on NRS revealed no significant differences between patients with an extraforaminal or an intraspinal lumbar disk herniation. This difference from published data may be due to the prospective investigation of our cohort, in contrast to the retrospective character of the earlier data.[5,7]

In addition to the treatment of pain, management further aims to reduce disability and to restore the patient's quality of life. The overall disability and quality of life did not differ between groups. Nevertheless, patients with extraforaminal disk herniation more frequently reported insomnia, possibly due to allodynia.

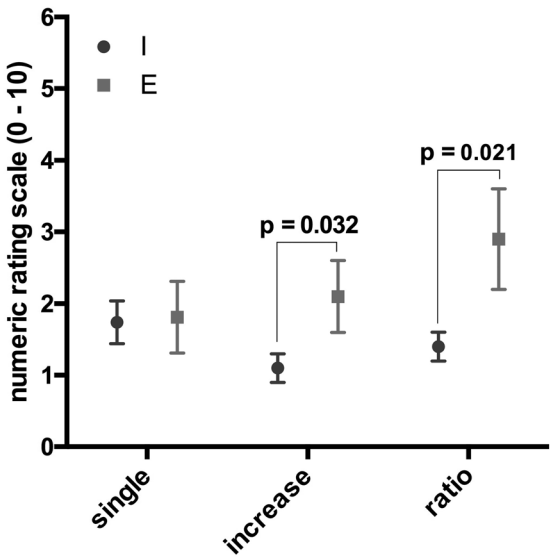

FIGURE 2. Analysis of wind-up ratio in patients with intraspinal (I) and extraforaminal (E) lumbar disk herniations. Data are presented as mean and standard error of the mean; p = significant difference.

Chronic pain disorders can be triggered by prolonged intensely painful stimuli. This may lead to neuroplastic changes of the central nervous system.[19] A decrease in gray matter of the brain and functional reorganization are commonly reported in chronic pain disorders.[20] Central sensitization can be triggered through increased excitability of dorsal horn neurons, which often occurs after tissue injury and inflammation.[21] Central sensitization can be assessed by WUR.[21,22] The enhancement of WUR can be detected in chronic pain conditions.[23] WUR was higher in patients with extraforaminal lumbar disk herniation. In addition, allodynia could be clinically detected in these patients, whereas it was absent in the intraspinal group. It is expected that the surgical intervention itself triggers neuropathic pain in extraforaminal lumbar disk herniation; however, as our results show, direct mechanical irritation of the susceptible dorsal root ganglion may also play a major role in the development of chronic pain.[5] *In vivo* studies showed that compression of a dorsal nerve root produced only an initial burst of wide dynamic range neurons, but compression of a dorsal root ganglion instead maintains repetitive activities throughout the period of compression.[24] Furthermore, chronic compression of a dorsal root ganglion was shown to enhance C-fiber response in a mouse model.[25]

QST can be used to study functional impairment of large myelinated, small myelinated, and unmyelinated fibers to document hyperalgesia and hypoesthesia. MDT and VDT evaluate the large myelinated A-alpha and A-beta sensory fibers, whereas the thermal testing modality assesses small myelinated and unmyelinated sensory nerve function. In addition, confirmatory studies have shown that non-nociceptive cool stimuli (CDT) are mediated by A-delta small myelinated fibers, and warm stimuli (WDT) and nociceptive (CPT, HPT) stimuli are mediated by C fibers.[26–28] Thermal QST results tend to show lower detection

thresholds in patients with an intraspinal disk herniation, but only the lower thresholds for cold temperatures reached statistical significance between groups. In contrast to our results, cold hypoesthesia rather than sensory gain was frequently found in patients with radiculopathy.[29,30] Differences in thermal thresholds were probably due to the different dermatomes investigated. Inconsistent findings have been reported concerning potential differences for thermal thresholds between the dermatome of the compressed nerve roots and the ipsilateral adjacent nerve root.[31,32]

In addition to the prospective character of our study, the combined use of QST and validated standardized comprehensive questionnaires were strengths of our study. Moreover, our study population was homogeneous, and patients with chronic pain, neurologic disorders, and major depression were excluded. However, the small patient cohort and the narrow inclusion and exclusion criteria may have led to selection bias.

In conclusion, extraforaminal compression is associated with chronic as well as neuropathic pain, presumably caused by direct compression of the dorsal root ganglion, which may preferentially promote specific chronic pain mechanisms.

Ethical publication statement: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The authors thank Tamara Wipplinger for proofreading the manuscript.

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