Redefining lumbar spinal stenosis as a developmental syndrome: an MRI-based multivariate analysis of findings in 709 patients throughout the 16- to 82-year age spectrum

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OBJECTIVE Using an imaging-based prospective comparative study of 709 eligible patients that was designed to assess lumbar spinal stenosis (LSS) in the ages between 16 and 82 years, the authors aimed to determine whether they could formulate radiological structural differences between the developmental and degenerative types of LSS.

METHODS MRI structural changes were prospectively reviewed from 2 age cohorts of patients: those who presented clinically before the age of 60 years and those who presented at 60 years or older. Categorical degeneration variables at L1–S1 segments were compared. A multivariate comparative analysis of global radiographic degenerative variables and spinal dimensions was conducted in both cohorts. The age at presentation was correlated as a covariable.

RESULTS A multivariate analysis demonstrated no significant between-groups differences in spinal canal dimensions and stenosis grades in any segments after age was adjusted for. There were no significant variances between the 2 cohorts in global degenerative variables, except at the L4–5 and L5–S1 segments, but with only small effect sizes. Age-related degeneration was found in the upper lumbar segments (L1–4) more than the lower lumbar segments (L4–S1). These findings challenge the notion that stenosis at L4–5 and L5–S1 is mainly associated with degenerative LSS.

CONCLUSIONS Integration of all the morphometric and qualitative characteristics of the 2 LSS cohorts provides evidence for a developmental background for LSS. Based on these findings the authors propose the concept of LSS as a developmental syndrome with superimposed degenerative changes. Further studies can be conducted to clarify the clinical definition of LSS and appropriate management approaches.

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KEYWORDS degenerative lumbar stenosis; developmental lumbar spinal stenosis; developmental syndrome

LUMBAR spinal stenosis (LSS) is one of the most commonly diagnosed spinal disorders in the adult population^{14,20,35} and can be categorized based on either the location of the pathology or the etiology of the stenosis.^{13,24,43} The most common type of LSS is degenerative and entails narrowing of the central canal, lateral recess, and/or neural foramen due to disc herniation, facet hypertrophy, ligamentum hypertrophy, and/or spondylolisthesis.^{13,24,43} Furthermore, the eligibility criteria for LSS are related to age demographics, and degenerative stenosis commonly presents after the age of 60 years.^{14,24,45}

On the other hand, developmental LSS entails nar-

rowing of the canal secondary to bone dysplasia.^{2,4,7,25,38,39} Arnoldi et al. initially defined developmental LSS as developmental narrowing of the spinal canal, with the early presentation of neurogenic symptoms and minimal radiological findings of degenerative spondylotic changes.²

Nearly all elderly patients exhibit radiological manifestations of spine degeneration. However, a relatively small percentage develop the clinical syndrome of spinal stenosis.^{14,20,24,35,45} Genetic polymorphisms may explain why some individuals are at a higher risk of developing symptomatic degenerative LSS, but this concept is only speculative and yet to be unraveled.^{4,18,22,24,26,30,31,34,41,42,45}

ABBREVIATIONS BCSA = vertebral body cross-sectional area; CCSA = spinal canal cross-sectional area; LSS = lumbar spinal stenosis; TDSS = total degenerative scale score.

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Although clinical examinations are often utilized to aid the diagnosis of LSS, imaging modalities, such as MRI, are necessary for a definitive diagnosis.^{2,4,6,7,13,14,24,25,35,45} Imaging modalities should be used judiciously, however, as radiographic findings of LSS do not always correlate with clinical findings, and they can be more extensive than the actual clinical scenario,^{6,13,14,20,24,35,45} as they may represent developmental rather than degenerative manifestations.^{6,12,14,20,24,35,45} In the degenerative LSS type, MRI findings represent the results of a spondylotic process culminating in the stenotic effect.^{14,20,24,35,45} Developmental LSS, on the other hand, starts with a smaller buffer.^{2,4,7,25,38–40} However, the morphological characteristics of lumbar segment components in the developmental LSS type are not well characterized.^{4,7,25,38–40}

We propose that reviewing the morphological manifestations throughout the age spectrum based on the MRI findings would provide further evidence of the natural history of the LSS development and help clearly define LSS types.

Methods

A prospective lumbar MRI study was conducted in clinically symptomatic LSS patients over the 16- to 82-year age spectrum. Patients were consecutively enrolled at a single institution and divided into 2 cohorts based on age demographics: patients presenting before the age of 60 years, and at the age of or after 60 years. A total of 709 patients met the inclusion criteria of clinically diagnosed neurogenic claudication, with varying degrees of pain, weakness, fatigability, and sensory changes for the duration of at least 2 months, followed by radiographic confirmation and diagnosis with MRI. Patients with axial back pain only, sacroiliac disorders, vascular claudication, trauma, tumor, or previous spinal surgery were excluded. The study was conducted under Cleveland Clinic institutional review board approval, and in accordance with that approval, all patients were evaluated after informed consent was obtained.

The 2 LSS cohorts were compared qualitatively and semi-quantitatively with an MRI radiographic analysis of lumbar segment components from L1 to S1. Sagittal T1-weighted spin-echo, sagittal T2-weighted fast spin-echo, and axial T2-weighted fast spin-echo (1.5-T) sequences were used for assessment in each case. All variables were analyzed by 2 spine fellowship-trained surgeons, who were blinded to classification types. The Schizas qualitative grading system was used to evaluate the extent of neural compression and severity of stenosis.³⁶ To be consistent with other degenerative grades in MRI radiological analysis, alphabet letters in the grades were converted to numbers (grades A–D were converted to numerical values of 1–4) (Table 1). Moreover, to minimize selection and inclusion bias, subtypes within the mild stenosis grade were excluded. Other variables tested included disc degeneration grades,⁴³ presence of disc herniation,⁹ disc height, endplate shape, irregularities and sclerosis, Schmorl's nodes,^{15,44} Modic changes,^{11,32} and facet degeneration grades.^{5,29,43} A chi-square test for independence was performed to compare the observed frequencies of degenerative categorical

TABLE 1. Results summary of the frequency of different Schizas grades of stenosis in the 2 age cohorts at L1–S1

Segment & Age Cohort	Grade 1	Grade 2	Grade 3	Grade 4	Grades 3 & 4*
L1–2					
<60 yrs	93.6%	2.3%	3.1%	0.2%	3.3%
≥60 yrs	88.2%	5.0%	4.5%	0.9%	5.4%
Total	91.9%	3.1%	3.5%	0.4%	3.9%
L2–3					
<60 yrs	79.5%	7.0%	10.3%	2.5%	12.8%
≥60 yrs	60.5%	10.9%	23.6%	4.1%	27.7%
Total	73.6%	8.2%	14.4%	3.0%	17.4%
L3–4					
<60 yrs	37.2%	9.2%	39.8%	13.3%	53.1%
≥60 yrs	20.9%	5.5%	53.2%	19.5%	72.7%
Total	32.1%	8.1%	44.0%	15.3%	59.3%
L4–5					
<60 yrs	4.7%	3.1%	49.9%	42.1%	92%
≥60 yrs	3.6%	3.6%	38.2%	54.5%	92.7%
Total	4.4%	3.3%	46.3%	46.0%	92.3%
L5–S1					
<60 yrs	62.6%	10.9%	17.2%	8.8%	26.0%
≥60 yrs	56.4%	15.9%	20.5%	6.4%	26.9%
Total	60.7%	12.4%	18.2%	8.1%	26.3%

Schizas grades A–D were converted to numerical values of 1–4.

* Combined percentage of grades 3 and 4 (severe stenosis).

variables between the 2 age cohorts, with specific emphasis on the effect size.

In exploring the between-groups differences of spinal canal dimensions, Pillai's trace statistic was used to determine the significance in multivariate testing; this statistic is more robust in analyzing data from samples of unequal size. Spinal canal dimensions were expressed as ratios with vertebral body dimensions to neutralize for a possible measurement bias due to ethnic, race, or body mass effects (Figs. 1 and 2).²⁵ A one-way between-groups multivariate analysis of variance was also conducted to include a total degenerative scale score (TDSS).¹⁹ This score, a continuous variable, is the summation of tested variable scores listed in (Table 2) with a potential range of 0–25, and with the Cronbach alpha coefficient for intra- and interobserver reliability testing reported as 0.829, suggesting reliable internal consistency in measurements.

Age was further controlled for as a covariate in the multivariate analysis mode. A p value ≤ 0.05 was accepted as indicating statistical significance. The statistical analyses were performed with IBM SPSS for Windows (version 22.0, IBM Corp.) statistical software.

Results

In our 709 patients that met the inclusion criteria, the mean age at presentation was 50.8 ± 12.85 years, with a normal distribution curve; 43.1% of the total cohort of patients were male, and 56.9% were females. Of the 709

FIG. 1. Sagittal T2-weighted MR image showing the measurement of anteroposterior spinal canal diameter (APC) and anteroposterior vertebral body diameter (APB).

patients, 480 (67.7%) were younger than 60 years (43.8% of these patients were male and 56.2% were female), and 229 (32.3%) were 60 years or older (41.6% male, 58.4% female).

Stenosis frequency and qualitative stenosis grades for both cohorts revealed that the L4–5 segment had the highest frequency of stenosis, followed by L3–4, then L5–S1 (Table 1). There was no significant association between the frequencies of stenosis grades and the 2 age cohorts at L5–S1, while there was a significant difference at L4–5 but with a small effect size (Table 2). These findings challenge the notion that stenotic changes at L4–5 and L5–S1 are mainly associated with a spondylotic, degenerative process.^{6–8,14,20,24,35}

The frequency of severe stenosis (combined percentages of Schizas³⁶ grades 3 and 4) at upper lumbar segments (L1–3) was higher for the older age cohort, whereas the frequency of severe stenosis at lower lumbar segments (L4–S1) was similar for both stenosis cohorts (Table 1). This difference implicates an age-related association with stenosis grades more influencing upper lumbar segments.

Decreasing spinal canal dimensions and the increasing frequencies of stenosis involvements down to L4–5 segments in all patients is contrary to the normal pattern of increasing spinal canal dimensions from L1 to L5 and implies a global maldevelopment of the spinal canal. This morphology was present in both cohorts (Tables 1 and 3).

FIG. 2. Axial MRI (T2-weighted) detailing lumbar spinal canal variables tested. **A:** Anteroposterior spinal canal length (APCa)/anteroposterior vertebral body length (APBa). **B:** Transverse spinal canal width (TCW)/transverse vertebral body width (TBW). **C:** Spinal canal cross-sectional area (CCSA)/vertebral body cross-sectional area (BCSA) with thecal sac cross-sectional area (TCSA)/CCSA. **D:** Interlaminar angle.

Multivariate analyses of quantitative variables concerned with relative spinal canal dimensions and areas on both sagittal and axial MR images revealed no significant differences between the 2 cohorts, except for the ratio of spinal canal cross-sectional area (CCSA) to vertebral body cross-sectional area (BCSA) at L2–3 with a small effect size ($p = 0.002$, partial eta-squared = 0.031). The age cohorts could only explain 3.1% of the variance in CCSA/BCSA at L2–3 (Table 3). There was a significant difference regarding the TDSS at L4–5 with a small effect size and at L5–S1 with a medium effect size. Inspection of the mean scores demonstrated that, compared to the younger cohort, the older age cohort had only a mild increase in the mean score (difference of 1.56) for L4–5 and a greater increase (difference of 1.8) for L5–S1.

Qualitative evaluation of spinal canal dimensions concerning posterior elements, facet inclination, and interlaminar angles assembled from axial MR images revealed identical spinal canal morphologies in the 2 cohorts.¹⁹ These commonalities of spinal canal morphologies imply a common developmental background.

The relevant data in this study suggest that the age-related lumbar intervertebral disc degeneration influences variable scores at the upper lumbar segments (L1–4) more than at the lower lumbar segments (L4–S1) (Table 2). This is contrary to what is commonly believed, as reported in the literature.^{2,4,6,7,13,24,25,27,45} At the lower lumbar segments, there were no significant differences between the 2 cohorts in the findings that were previously thought to be characteristic of age-associated degeneration, such as disc herniation, loss of disc height, endplate changes, and Schmorl's nodes (Table 2).^{5,8,9,11,15,29,32,43,44} The frequency of radiological degeneration in the facet joints was high in both cohorts (65%–80%). There was a significant

TABLE 2. Pearson's chi-square test for independence (or with Yates' correction for continuity) with special emphasis on the effect size (strength of association) between the tested variable and age cohorts at L1–S1

Variable & Level	χ^2	p Value	Cramer's V Value or Phi Coefficient (effect size)
Pfirsman's degenerative disc grades			
L1–2	132.9	<0.005	0.34 (medium)
L2–3	106.6	<0.005	0.38 (medium)
L3–4	83.4	<0.005	0.34 (medium)
L4–5	33.4	<0.005	0.21 (small)
L5–S1	33.4	<0.005	0.21 (small)
Pathria's facet degenerative grades ^{29,43}			
L1–2	18.98	<0.005	0.16 (small)
L2–3	29.32	<0.005	0.20 (small)
L3–4	21.37	<0.005	0.17 (small)
L4–5	16.16	0.001	0.15 (small)
L5–S1	8.08	0.044	0.11 (small)
Schizas' qualitative stenosis grades ³⁶			
L1–2	7.29	0.121	0.10
L2–3	30.44	<0.005	0.21 (small)
L3–4	25.78	<0.005	0.19 (small)
L4–5	10.612	0.031	0.12 (small)
L5–S1	6.718	0.15	0.09
Endplate shape & irregularity			
L1–2	23.47	<0.005	0.18 (small)
L2–3	25.00	<0.005	0.18 (small)
L3–4	17.76	<0.005	0.16 (small)
L4–5	2.84	0.417	0.06
L5–S1	5.412	0.144	0.08
Disc height divided into quarters compared to reference normal disc height level			
L1–2	9.63	0.022	0.10 (small)
L2–3	13.13	0.004	0.10 (small)
L3–4	3.57	0.312	0.07
L4–5	11.65	0.009	0.13 (small)
L5–S1	14.17	0.003	0.14 (small)
Modic endplate changes ^{11,32}			
L1–2	9.31	0.025	0.11 (small)
L2–3	9.39	0.052	0.11 (small)
L3–4	13.69	0.008	0.13 (small)
L4–5	3.02	0.555	0.06
L5–S1	13.29	0.010	0.13 (small)

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TABLE 2. Pearson's chi-square test for independence (or with Yates' correction for continuity) with special emphasis on the effect size (strength of association) between the tested variable and age cohorts at L1–S1

Variable & Level	χ^2	p Value	Cramer's V Value or Phi Coefficient (effect size)
Schmorl's nodes ^{15,44} frequency difference, w/ Yates' continuity correction			
L1–2	0.08	0.778	–0.01
L2–3	5.43	0.020	–0.09 (small)
L3–4	3.43	0.064	–0.04
L4–5	0.99	0.319	–0.04
L5–S1	0.10	0.75	–0.023
Disc hernias ⁹ frequency difference, w/ Yates' continuity correction			
L1–2	0.22	0.641	0.023
L2–3	5.03	0.025	0.09 (small)
L3–4	0.00	1.00	0.001
L4–5	1.19	0.315	–0.041
L5–S1	3.366	0.067	–0.072

Effect size statistics utilizing Cramer's V or phi correlation coefficient (for 2 by 2 tables).

difference in facet degeneration grades across all lumbar segments with a statistically small effect size (Table 2). The weak association between the stenosis types and facet degeneration grades in all lumbar segments makes radiological differences essentially irrelevant to either stenosis type.

The L5–S1 segment in this study was shown to have peculiar characteristics. Stenosis frequency was lower at L5–S1 than at the adjacent L3–5 segments (Tables 1 and 2). Our study results showed lower frequencies of all degeneration variables compared with adjacent L3–5 segments regardless of the age cohorts. This should be accounted for by the coronal orientation of the L5–S1 facet joints. However, the lower incidence of stenosis at L5–S1 challenges the notion that local biomechanical environment influences degeneration.³³

Furthermore, a one-way between-groups multivariate analysis of covariance was performed to investigate differences between the 2 cohorts while statistically controlling for age. Age was assumed to influence spinal canal dimensions for the older age cohort. Preliminary checks were conducted to ensure that there was no violation of the assumptions. After adjusting for age there was no significant difference between the 2 cohorts with respect to vertebral dimensions and qualitative stenosis grading.

Discussion

The radiological findings and data analysis from our study suggest that radiological manifestations of a narrow

TABLE 3. Results of one-way between-groups multivariate analysis of variance with adjusted alpha level

Level	Pillai's Test Value	p Value	Tests of Between-Groups Effects
L1–2	0.071	0.132	No significant difference
L2–3	0.054	0.037	CCSA/BCSA: $F = 9.682$, $p = 0.002$, $\eta^2 = 0.020$ (small effect size)
L3–4	0.026	0.209	No significant difference
L4–5	0.065	<0.005	TDSS: $F = 26.93$, $p < 0.05$, $\eta^2 = 0.056$
L5–S1	0.114	<0.005	TDSS: $F = 28.67$, $p < 0.05$, $\eta^2 = 0.079$

η^2 = partial eta-squared.

A p value < 0.05 indicates a significant difference between the 2 age cohorts on the combination of dependent variables. The variables listed are the only ones that showed a significant difference on multivariate analysis.

spinal canal in the younger age cohort cannot be attributed to degeneration only. Furthermore, the age at presentation and the natural history of the LSS syndrome are largely unpredictable and are further compounded by the neural tissue tolerance to the combined effects of central stenosis.^{20,35}

In our study, there was no significant difference of quantitative spinal canal characteristics tested between the 2 cohorts. Age-related degenerative radiological changes influenced upper lumbar segments L1–4 rather than lower segments L4–S1. There was no or only minimal significant difference in degenerative radiological variables and stenosis grades between the 2 cohorts at segments commonly involved with stenosis (L3–5).

These findings cast doubt on degeneration as the only etiopathology, and any attempt to formulate a clear differentiation between the 2 cohorts is challenging. Spinal canal development, however, starts early in life.^{3,16,17,21,23} and recent studies implicated a genetic background for lumbar central stenosis.^{1,4,12,18,21,23,27,28,30,31,34,37,41,42} Battié et al. demonstrated that central LSS is highly genetic and that disc degeneration and height appear to represent one pathway through which genes influence spinal canal dimensions.⁴ A plausible theory is to rely on the developmental concept.^{4,7,25,31,34,38–42} We propose through our findings that a developmentally narrow spinal canal is the basic characteristic that predisposes patients to develop the clinical syndrome in LSS.

A developmental and degenerative etiology, however, can exist in the same patient.^{2,4,7,25,27,38–40} In other words, a developmental foundation is compounded by further degeneration. This is likely very common, thus confusing the overall etiological picture and blurring the boundaries between the 2 entities.^{2,4,25,27} This is reflective of the conflict in the literature regarding the poorly defined developmental stenosis.^{2,4,25,27} The high rate of disc hernias or hypertrophic facets at segments commonly involved with stenosis (L3–4 and L4–5) may induce the clinical syndrome in an asymptomatic patient at a younger age. This may gain importance in the modern era of interest in minimum access spine surgery (MIS). It is likely uncertain whether these patients should undergo discectomy only via an MIS approach or would need more aggressive decompression.^{9,27}

The basic pathoanatomy in developmental stenosis is related to the confined spaces available for neural elements.^{2,4,6,7,13,14,24,25,35,45} Recently, Luk and Samartzis³⁰ in-

troduced the concept of lumbar intervertebral disc “dys-generation,” defined as early identification of a black or unhydrated or dehydrated disc, with characteristics that vary from those of lumbar intervertebral disc degeneration. In our study basic radiological manifestations of lumbar components in the younger age cohort may represent potential failure of full development early in life. Such radiological manifestations are likely to persist throughout the life span. Radiological degenerative manifestations in younger patients should be interpreted with caution to avoid the overuse of fusion. Similarly, the lower frequency of stenosis and degeneration at L5–S1 has a particular significance concerning the need for incorporation of the lumbosacral segment in spine fusions.

The importance of defining LSS as a developmental syndrome cannot be overemphasized. Defining LSS subtypes according to surface radiological measurements only is a shortcoming. Radiological degenerative and dysgenerative manifestations in the developmental LSS subtype are poorly characterized in the literature.^{1–14} To the best of our knowledge, this is the first large-scale study to compare spinal canal morphometric parameters as well as lumbar degenerative manifestations between younger and older cohorts. Comparative analysis of the 2 age cohorts demonstrated no or minimal significant difference in the radiological degeneration of the lumbar segment components. Our study showed that the biological age of a stenotic lumbar segment does not correlate with the actual chronologic age of the patient. Redefining lumbar stenosis as a developmental syndrome regardless of radiological findings mandates further studies to define “true superimposed degeneration.” Such re-definition is likely to influence clinical decision-making and fusion indications. From an analytical perspective, the use of a defined clinical syndrome is essential for recruiting specific and homogeneous patient populations in validated clinical trials.¹⁴

Our study was not without limitations. Lower segments may have undergone significant degenerative changes earlier, such that differences cannot be detected with a cutoff at 60 years of age. Age group stratification or further longitudinal study is warranted to assess the natural history of development. Schizas qualitative grading was utilized in the study for radiologic confirmation of included LSS cases. It takes into account the more relevant root-to-CSF ratio indicating neural compression. Direct surface measurements for LSS confirmation are controversial in the literature and, alone, fail to take into account the more

relevant root-CSF ratio.³⁶ Moreover, the study design prevents inferring sound attributes of pain correlation with lumbar MRI changes analyzed. Although our results support a developmental origin for the subset of MRI changes, a developmental causality can only be suggested.

Conclusions

Integration of all the morphometric and qualitative characteristics of the 2 LSS cohorts provides evidence for a developmental background for LSS. With such findings we propose the concept of LSS as a developmental syndrome with superimposed degenerative changes. Further longitudinal studies to assess the natural history of development and to clarify the clinical definition of LSS and management approaches should be appropriate.

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Author Contributions

Conception and design: all authors. Acquisition of data: Kitab, Lee. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Benzel. Study supervision: Benzel.

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