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Comparison of vertebral and intervertebral disc lesions in aging humans and rhesus monkeys

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SUMMARY

Objective: To compare gross and histologic patterns of age-related degeneration within the intervertebral disc and adjacent vertebra between rhesus monkeys and humans.
Materials and methods: We examined age-related patterns of disc degeneration from mid-sagittal sections of the intervertebral disc and adjacent vertebral bodies (VB) among six rhesus monkey thoracolumbar and seven human lumbar spines. Gross morphology and histopathology were assessed via the Thompson grading scheme and other degenerative features of the disc and adjacent bone.
Results: Thompson grades ranged from 3 through 5 for rhesus monkey discs (T9–L1) and 2 through 5 for the human discs (T12–S1). In both rhesus monkey and human discs, presence of distinct lesions was positively associated with Thompson grade of the overall segment. Degenerative patterns differed for radial tears, which were more prevalent with advanced disc degeneration in humans only. Additionally, compared to the more uniform anteroposterior disc degeneration patterns of humans, rhesus monkeys showed more severe osteophytosis and degeneration on the anterior border of the vertebral column.
Conclusions: Rhesus monkey spines evaluated in the present study appear to develop age-related patterns of disc degeneration similar to humans. One exception is the absence of an association between radial tears and disc degeneration, which could reflect species-specific differences in posture and spinal curvature. Considering rhesus monkeys demonstrate similar patterns of disc degeneration, and age at a faster rate than humans, these findings suggest longitudinal studies of rhesus monkeys may be a valuable model for better understanding the progression of human age-related spinal osteoarthritis (OA) and disc degeneration.

Introduction

Intervertebral disc degeneration and spinal osteoarthritis (OA) are age-related processes that underlie several painful disorders of the spine in humans. The prevalence of age-related spinal OA has been shown to be as high as 85%[1] and some degree of disc degeneration appears to be present in all adults[2]. Considering the high economic impact (from both health care services and absence from the workplace) associated with disc degeneration and its complications[3,4], strong interest in improving the understanding of the etiology of disc degeneration and in developing new therapies exists.

A major challenge in investigating the etiology of disc degeneration and in evaluating new therapies is selecting a suitable animal model that mimics the morphology and progression of age-related disc degeneration of humans[5,6]. In most animal models, for example, disc degeneration does not occur naturally and must be artificially induced. Even in animal models that do develop disc degeneration naturally (e.g., sand rats[7] and various canines[8]), differences in spine morphology and biomechanics can make it difficult to extrapolate the findings to humans.

The rhesus monkey (*Macaca mulatta*) is a non-human primate that shares genetic, anatomical, and biomechanical similarities with humans[9,10]. Although rhesus monkeys are technically quadrupedal and ambulate on four legs, they load their spines similar to humans when sitting[11]. Captive rhesus monkeys have an average lifespan of 27 years and maximal lifespan of 40 years[12]. Interestingly, the rhesus monkey naturally develops polyarticular OA with age[13,14] (Fig. 1). The aging spines of rhesus monkeys are

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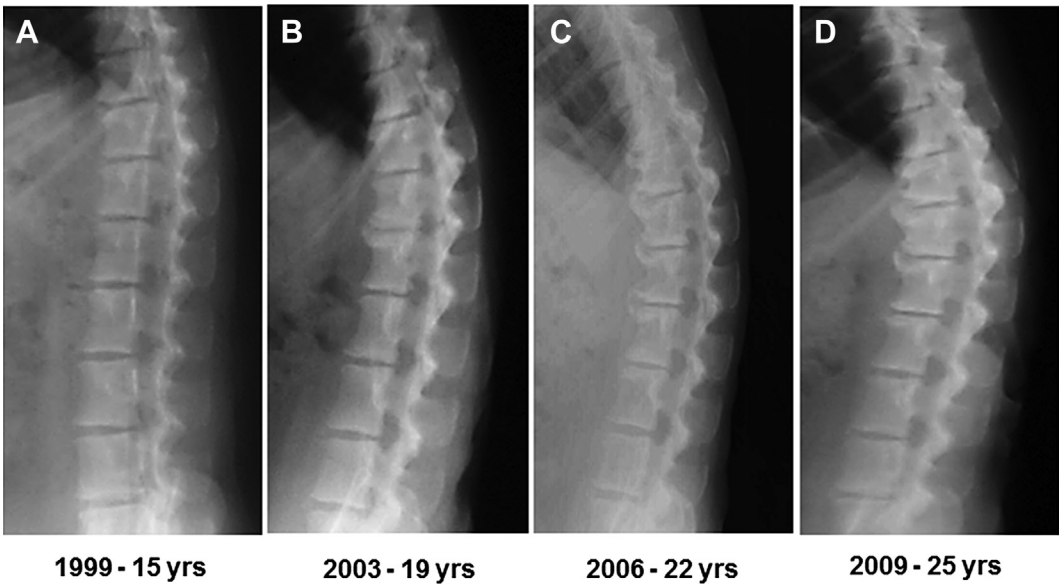

Fig. 1. A through D are lateral radiographs of the thoracolumbar spine from an individual rhesus monkey used in this study. Radiographs span 10 years and depict increasing osteophytosis and disc space narrowing with age. Note, rhesus monkeys typically have seven lumbar vertebrae.

afflicted with disc degeneration, osteophytosis, and kyphosis. As in humans, these degenerative changes are most severe in the thoracolumbar and lumbosacral zones[2,15,16]. Although this suggests that rhesus monkeys exhibit similar anatomic patterns of disc degeneration as humans, it remains unclear whether rhesus monkeys exhibit similar histologic features of disc degeneration as well. If the histologic progression of spinal OA and disc degeneration in rhesus monkeys is comparable to that of humans, utilizing monkeys as an animal model for disc degeneration in basic science and preclinical studies is potentially appropriate. The objective of this study was, therefore, to compare the process of age-related degeneration within the intervertebral disc and adjacent vertebra between rhesus monkeys and humans.

Materials and methods

Study design

We used the Thompson grading scheme to create scores to compare the progression of disc degeneration between humans and rhesus monkeys. Thompson grades are a gross measure of disc degeneration across five categories based on the accumulation of tissue pathologies in and adjacent to the disc[17]. See methods from Thompson *et al.*, 1990 for thorough description of grading. Consequently, the Thompson grade provides an overall measure of gross degeneration of the disc segment that is independent of chronological age, which is necessary for our study because humans and rhesus monkeys age at different rates. Also, both the rhesus monkey and human samples are samples of convenience and, therefore, are not matched for age or degree of degeneration. Fig. 2 indicates Thompson grading scheme in relation to the rhesus monkeys and human disc segments in this study.

Monkey spines

The rhesus monkeys used in this study were part of a longitudinal study of the effect of caloric restriction on mortality, the details of this study have been described elsewhere[18–20]. Monkeys were housed indoors in single cages in a temperature-controlled environment and fed two meals a day (0700 and 1400 h). Following natural death, thoracolumbar spines were harvested and stored at −80°C. Six spines, spanning mid-thoracic to upper lumbar (T9–L2) from three female and three male rhesus monkeys (aged 19.4–36.1 years with a mean age of 28.0 years), were randomly selected from this collection for evaluation in the current study. The NIH Animal Center in Poolesville, MD, is fully accredited by the American Association for Accreditation of Laboratory Animal Care, and all procedures were approved by the Animal Care and Use Committee of the NIA Intramural Program.

Human spines

Lumbar spines (T11–S1) were obtained from seven human cadavers (UCSF Willed Body Program), including two females and five males with ages ranging from 51 to 67 years with a mean age of 60.3. Tissue was then stored at −80°C and did not thaw until further dissection and preparation in the Orthopaedic Research Laboratory at the University of California, San Francisco.

Tissue processing and histology

Spines from the human cadavers and rhesus monkeys were processed for histology using similar procedures. Paraspinal soft tissues and posterior elements were removed from the spinal column. The spinal column was then sectioned into parasagittal slabs (1 cm thick). One midsagittal slab from each spine was further separated into individual motion segments (rhesus monkeys, $n = 18$; humans, $n = 44$), which comprised whole discs with 3–4 cm of bone from the adjacent vertebrae. Each motion segment was then fixed using 10% neutral buffered formalin (Thermo Fisher Scientific). Segments were photographed and then decalcified with Ion Exchange Decal, a mild but rapid ion exchange decalcifier (BioCare Medical), until a radiographic endpoint test confirmed the specimens devoid of calcium. Segments were dehydrated in an ascending series of ethanol and cleared with Clearite 3 (Richard Allen), then infiltrated and embedded in paraffin wax. Once sectioned and mounted on slides, serial sections were stained with Mallory–Heidenhain[21] and Safranin-O.