The pathogenesis of discogenic low back pain

B. Peng, W. Wu, S. Hou, P. Li, C. Zhang, Y. Yang

From 304th Hospital, Beijing, People’s Republic of China

Discogenic low back pain is a common cause of disability, but its pathogenesis is poorly understood. We collected 19 specimens of lumbar intervertebral discs from 17 patients with discogenic low back pain during posterior lumbar interbody fusion, 12 from physiologically ageing discs and ten from normal control discs. We investigated the histological features and assessed the immunoreactive activity of neurofilament (NF200) and neuropeptides such as substance P (SP) and vasoactive-intestinal peptide (VIP) in the nerve fibres.

The distinct histological characteristic of the painful disc was the formation of a zone of vascularised granulation tissue from the nucleus pulposus to the outer part of the annulus fibrosus along the edges of the fissures. SP-, NF- and VIP-immunoreactive nerve fibres in the painful discs were more extensive than in the control discs. Growth of nerves deep into the annulus fibrosus and nucleus pulposus was observed mainly along the zone of granulation tissue in the painful discs. This suggests that the zone of granulation tissue with extensive innervation along the tears in the posterior part of the painful disc may be responsible for causing the pain of discography and of discogenic low back pain.

Discogenic low back pain is non-radicular and occurs in the absence of spinal deformity, instability and signs of neural tension.1 It arises from the disc itself2 and the mechanism of its production is uncertain.

In the absence of evidence of disc pathology on radiological and CT images, it may be impossible to localise a painful disc from the symptoms and the signs elicited on physical examination. Although MRI may identify a degenerative disc (a ‘black disc’), it will not differentiate between a disc which is pathologically painful and one which is physiologically ageing.3 Intervertebral disc degeneration is commonly seen on MRI in asymptomatic subjects.4-6 Discography is the most important test for diagnosing discogenic back pain. Some believe that discography, when carefully done and interpreted, is highly specific with a false-positive rate of 0%.7 However, controversy remains as to the accuracy and specificity of discography because of the inability to understand the mechanism which produces the pain. That provoked by the injection of contrast medium into the disc may be difficult to relate to the images seen after discography. The key feature of discography is the reproduction of the pain felt by the patient on stimulation of the disc.8 Studies have shown that reproduction of the pain is associated with tears which extend to the outer region of the annulus fibrosus.9-11 This suggests that the origins of the pain in discography may lie in abnormalities of the structure of the disc. In particular, the pain may arise from the tears and surrounding structures into which the contrast medium leaks from the nucleus pulposus into the outer zone of the annulus fibrosus. Thus, discography may be helpful in understanding the pathophysiology of discogenic low back pain.

The contrast-enhanced axial view of CT after discography allows visualisation of the tears in the painful disc. With this information we have been able to localise and excise en bloc specimens of the torn annulus of a painful disc during posterior lumbar interbody fusion for discogenic low back pain (Fig. 1). Consecutive slices of the excised specimen have been studied histologically and immunohistochemically to explore the intrinsic relationship between the pathological lesions and the surrounding innervation in a painful disc.

The distribution of nerve fibres in the different parts of the human disc has been previously described.12-14 The nerve fibres may contain nociceptive neurotransmitters such as substance P (SP), calcitonin-gene-related peptide (CGRP), and vasoactive intestinal peptide (VIP).15-18 However, there has been no description of nerve ingrowth along the tears or fis-
sures in a painful disc. Our aim was to investigate the pathological changes in and the innervation of painful discs in order to understand the cause and the mechanism of primary discogenic low back pain.

**Patients and Methods**

We examined 19 specimens of lumbar discs taken from 17 consecutive patients with disabling discogenic low back pain who underwent excision of the disc and posterior lumbar interbody fusion (PLIF). There were 12 men and five women, with a mean age of 36 years (19 to 55). The mean duration of low back pain was 29 months (8 to 120). Six patients had a history of lumbar injury. All had conventional radiography and MRI of the lumbar spine. None had symptoms or signs of radicular pain and disc herniation was not seen on MRI. All the patients had discography before operation. A positive discogram was seen in a patient with an annular tear who had a severe concordant pain response. After discography, CT was performed to localise the tear in the painful disc. In the 19 painful discs, there were 17 annular tears occurring posteriorly or posterolaterally and two seen both anteriorly and posteriorly. The signal intensity on T2-weighted MRI was decreased in 18 of the painful discs, with only one appearing to be relatively normal.

For a normal control group we obtained ten specimens from the posterior parts of disc tissue at L4-L5 and L5-S1 from five fresh cadavers with a mean age of 36 years (19 to 55), who had had no history of low back pain during their lifetime. All the patients had discography before operation. A positive discogram was seen in a patient with an annular tear who had a severe concordant pain response. After discography, CT was performed to localise the tear in the painful disc. In the 19 painful discs, there were 17 annular tears occurring posteriorly or posterolaterally and two seen both anteriorly and posteriorly. The signal intensity on T2-weighted MRI was decreased in 18 of the painful discs, with only one appearing to be relatively normal.

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Histological examination. In the normal control specimens, the annulus fibrosus consisted of the normal lamellar structure of collagen fibres. The nucleus pulposus showed sparse collagen fibres with a single cartilage cell or an island of a few cells surrounded by a capsule. Blood vessels were seen in the posterior longitudinal ligament and the outermost layers of the annulus fibrosus. In the specimens of physiologically ageing discs, the lamellar structures of the annulus fibrosus were arrayed relatively regularly, and, in some
samples, disrupted and confused lamellar structures were seen in the middle and inner layers of the annulus fibrosus. In the nucleus pulposus, there was increased density of the matrix and the formation of clusters of chondrocytes. The distinction between the nucleus pulposus and the inner annular fibrous became blurred, and there was a tendency for this to become more evident with increasing age.

In the specimens of painful discs from the patients with discogenic low back pain, the most notable feature was the formation of a zone of vascularised granulation tissue which extended from the nucleus pulposus to the outer region of the annulus fibrosus along the tears shown on CT after discography (Fig. 2). The degree of maturation of the granulation tissue varied. The zone was approximately 0.1 to 5 mm in sagittal width and contained one or several fissures. The adjacent tissues surrounding the tears in the posterior part of the nucleus pulposus and the annulus fibrosus were replaced by disorganised and vascularised granulation and scar tissue. The lamellar structure of the annulus fibrosus adjacent to the zone of granulation tissue was arrayed relatively regularly, becoming disrupted and confused. The structure of the annulus fibrosus distant to this zone was relatively normal. Extensive vascularity was seen in the outer layers of the annulus fibrosus. The distinction between the nucleus pulposus and the inner annulus fibrosus had disappeared. In the nucleus pulposus, fibrosis and increased density of the matrix were observed. The round chondrocytes were transformed into oval fibroblasts.

**Immunohistochemical examination for innervation.** The number and percentage of SP-, NF- and VIP-immunoreactive nerve fibres in the specimens of control discs, ageing discs, and painful discs varied (Table I). By observing consecutive tissue sections, specific immunoreactivity to NF, SP and VIP was seen in the same nerve fibres. When NF immunoreactivity was observed, a response to one or both of the two neuropeptides was seen simultaneously. Both bundles of nerve fibres and free fibres were seen in the painful and control discs, and myelinated and unmyelinated free fibres were identified. Some immunoreactive dots may have been images of cross-sections of nerve fibres. No immuno-
reactive structures were seen in the sections treated with normal serum only, in the absence of primary antibody.

In all the control, ageing, and painful discs, the posterior longitudinal ligaments contained NF-staining nerve fibres. In control discs sparse nerve fibres were seen only in the outermost layers of the annulus fibrosus. Positive staining for SP was present in three (30%) of the ten control specimens, for NF in four (40%), and for VIP in two (20%). Occasionally, VIP-immunoreactive fibres were found adjacent to blood vessels. Positive staining for SP, NF, and VIP increased in the specimens of the ageing discs and those which were painful. In the ageing discs, NF-positive stain-

### Table I. SP-, NF- and VIP-immunoreactive fibres in the groups of discs, by number and percentage (C, normal control disc (10); A, ageing disc (12); and P, painful disc (19))

<table>
<thead>
<tr>
<th>Area</th>
<th>SP</th>
<th>NF</th>
<th>VIP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>A</td>
<td>P</td>
</tr>
<tr>
<td>PLL, 1/3 in AF</td>
<td>5 (50)</td>
<td>9 (75)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Outer 2/3 in AF</td>
<td>3 (30)</td>
<td>5 (42)</td>
<td>12 (63)</td>
</tr>
<tr>
<td>Inner 2/3 in AF</td>
<td>0</td>
<td>0</td>
<td>6 (32)</td>
</tr>
<tr>
<td>NP</td>
<td>0</td>
<td>0</td>
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* PLL, posterior longitudinal ligament; AF, annulus fibrosus; NP, nucleus pulposus

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Photomicrographs showing evidence of innervation in painful discs. Figure 3a – SP-immunoreactive nerve fibres (arrows) are present in the margin of the tear (T) within the annulus fibrosus (x130). Figure 3b – SP-immunoreactive nerve fibres (arrows) are seen in the granulation tissue within the nucleus pulposus (x130). Figure 3c – NF-immunoreactive nerve fibres (arrows) are present in the margin of the tear within the annulus fibrosus (x130). Figure 3d – VIP-immunoreactive nerve fibres (arrows) are present in the annulus fibrosus (haematoxylin and eosin; x270).
ing nerve fibres were observed growing into the inner annulus fibrosus in two (17%), but SP and VIP fibres were neither seen in the deeper part of the annulus fibrosus nor in the nucleus pulposus. Such ingrowth into these deeper sites in painful discs occurred mainly along the zone of granulation tissue around the tears (Fig. 3). SP- and NF-immunoreactive fibres were present in the margin along the tears. In the painful discs, positive staining for SP and NF in the nucleus pulposus was observed in four (21%) and six (32%), respectively, showing ingrowth of nerve into the nucleus pulposus, but no VIP-positive staining was noted.

Discussion

Many studies have suggested that nerve fibres are present in the longitudinal ligaments and in the outer layers of the annulus fibrosus. An immunohistochemical study demonstrated the presence of SP-immunoreactive fibres in the posterior longitudinal ligament and the presence of SP-, CGRP-, and VIP-immunoreactive nerve fibres has been demonstrated in animal and human intervertebral discs. However, these studies were only carried out on normal lumbar discs. There have been further investigations concerning the innervation of discs in the patients with low back pain. These were on specimens harvested from the anterior aspect of painful discs, in which tears or fissures in the annulus fibrosus are rarely seen on discography. Hence, these investigations were not able to define accurately the structures from which low back pain and the pain provoked by discography may originate.

Studies by CT after discography have suggested that the contrast media leaks from the nucleus pulposus to the posterior part of the annulus fibrosus along the tears in painful discs and therefore may be attributable to weakness in the posterior annulus fibrosus. Previous studies have indicated that pain induced by discography is associated with tears which extend to the outer zone of the annulus fibrosus. Our study examined specimens of painful discs taken from the posterior part of the annulus, including tears shown on CT after discography.

There are two theories concerning the mechanism of pain on discography. One attributes this to the stimulation of nociceptive fibres in the innervated part of the annulus fibrosus, the vertebral end plate or body, which may cause pain as the injection increases intradiscal pressure. Another view is that injection leads to chemical stimulation accompanying the ingrowth of granulation tissue. An extensive network of nerve fibres was seen in the posterior part of the annulus fibrosus in the ageing discs, but there was no pain since there were no tears and no surrounding granulation tissue in this region of the annulus fibrosus.

A normal disc should have a bright appearance on MRI, whereas a dehydrated disc appears dark. The latter may be the earliest stage of degenerative disc disease. However, it may reflect the normal physiological process of ageing and not be associated with any disease process. Abnormalities of the disc are commonly seen on MRI in asymptomatic subjects. Modic et al found that an abnormal signal intensity was present in 30% of the discs in asymptomatic volunteers. It is difficult to distinguish the ageing disc from the pathological disc but the presence of a zone of vascularised granulation tissue accompanying the nociceptors along the tears of the annulus fibrosus is an almost constant finding in a pathological disc.

Of the 17 patients with discogenic low back pain in our study, six were adults below the age of 30 years. It is unlikely that the changes in their discs were age-related, but injury to the posterior annulus fibrosus may have played a role in their pathogenesis. Structurally, the weak posterior part of the annulus fibrosus may be subjected to damage, and it is a consistent site for tears shown on discography. Different animal models of the annular defect have shown that the healing is defective and probably initiates degeneration of the disc. The tears demonstrated at the periphery of the annulus fibrosus may play a critical role in discogenic low back pain and the initiation of degenerative changes. The formation of vascularised granulation tissue may be a physiological response to repair the injury to the annulus. However, because of the poor blood supply and the high tensile stress, inadequate healing seems to be inevitable. Immunoreaction and the recruitment of inflammatory cells may impede healing further, and the ingrowth of vascularised granulation tissue into the disc may produce growth factors and cytokines which may modulate the differentiation of cells such as chondrocytes in the nucleus pulposus. These may be transformed into fibroblasts leading to degeneration of the disc. In some patients these changes may be the principal cause of this back pain, and may be a contributory factor in other patients.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.
References

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