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Topical review

Discogenic pain

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Lumbar disc disease characterized by symptomatic disc herniation or typical sciatica is a major challenge for health care. Its prevalence was studied as part of the Mini-Finland Health Survey in a sample of over 7000 Finnish adults. A diagnosis of lumbar disc syndrome based on medical history, symptoms, and standardized physical examination was made for 5.1% of the men and for 3.7% of the women. One third of all patients with lumbar disc syndrome had been previously hospitalized with it, and one fifth of the patients had undergone lumbar surgery. About 6% of the population's work disability was estimated to be attributable to lumbar disc syndrome (Heliövaara et al., 1987).

Beyond the more specific herniation problem, discogenic origin has been assumed to be a major cause of non-specific low back pain (LBP). In a population of chronic LBP patients 39% had an internal disc disruption, with concordant pain provocation in discography indicating the discogenic origin of their pain (Schwarzer et al., 1995). Furthermore, disc degeneration is considered to be the initiating event that leads to secondary deterioration of the facets, ligaments, and muscles.

The spine and discs in particular are very specific both anatomically and functionally compared with the peripheral joints. While degenerative knee changes are relatively rare in elderly people, nearly all exhibit disc and spinal degeneration. Additionally, while few subjects with severe gonarthoris are asymptomatic, the reverse holds true for many people with severe degenerative spinal changes. Furthermore, the findings of degenerative images on MRI of symptom-free subjects do not predict subsequent complaints even after several years (Borenstein et al., 2001). These findings illustrate why we need a more comprehensive understanding of the mechanisms of asymptomatic disc degeneration and discogenic pain.

1. Disc degeneration

Michael Adams suggested that endplate damage would precede disc degeneration (Adams et al., 2000). Diminished blood supply in the endplate initiates tissue breakdown, firstly in the endplate and thereafter in the nucleus in the first half of the second life decade (Boos et al., 2002). It is worth mentioning that radial tears were visible in the nucleus in the age group 11–16 years. This is the age when the first low back disease symptoms and hospitalizations are encountered (Taimela et al., 1997).

The first matrix changes occur in the center of the nucleus and include fragmentation of proteoglycans followed by decreases in proteoglycan and water concentrations and a decline in the number of viable cells (Buckwalter, 1995). The proteoglycans of the endplate regulate the movement of solutes into and out of the disc (Roberts et al., 1996). The removal of proteoglycans from the endplate accelerates the loss of proteoglycans from the nucleus. Reduced lumbar artery blood flow may also diminish nutrition through the endplates. Indeed, an association between atherosclerosis and aortic calcification, reduced lumbar artery blood flow, increased incidence of disc degeneration, and subjective LBP has been shown (Kauppila et al., 1997).

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2. Intervertebral disc as a pain generator

A tissue or structure can generate pain only if it is innervated. In a normal human lumbar disc, nerve endings can be found only in the periphery of the outer annulus, at a depth of, at most, a few millimeters (Ashton et al., 1994). Similarly, the perianular connective tissue and the central endplate are the most densely innervated structures in a normal ovine disc, although the innervation is meager and limited to the very outermost structures (Fagan et al., 2003). However, in highly degenerated discs nerves may even penetrate into the nucleus pulposus (Freemont et al., 1997). Most of these nerve fibers, which are identified by immunochemistry, accompany blood vessels relating probably to vaso-regulation. Another set of neural structures, independent of vessels, has been found in the nucleus of painful discs assessed by the provocative discography of patients undergoing anterior fusion surgery for chronic LBP. These neural structures express substance P and have a morphology of nociceptive nerve terminals. These findings emphasize the role of the nerve terminals of the degenerated disc in the pathology of back pain, and make the distinction between painful disc disease and non-painful disc degeneration more understandable.

Discography has traditionally been regarded as the gold standard for the diagnosis of discogenic pain. Discographic studies have shown that only annular ruptures extending to the outer annulus produce exact or similar pain to that previously experienced (Moneta et al., 1994). It is important to note that intervertebral disc degeneration per se is not painful, and disc degeneration is frequently observed in asymptomatic subjects (Borenstein et al., 2001). However, MRI-confirmed disc degeneration at the age of 15 increased the risk of persistent LBP 16-fold (Salminen et al., 1999). Among adults the corresponding relationship is not observed.

Discography has been used widely to study the MRI phenotype of patients with discogenic pain. In addition to annular ruptures, potential 'discogenic signs' on MRI include high intensity zone (HIZ) lesions and endplate degeneration, i.e. Modic changes (Modic et al., 1988). The relevance of HIZ lesions as indicators of discogenic pain has been questioned lately (Carragee et al., 2000), whereas Modic changes seem to be more feasible imaging signs of discogenic pain (Braithwaite et al., 1998).

The mechanical consequences of disc degeneration include the loss of disc height and segmental instability, increase in the loads of the facets generating subluxations, and cartilage changes, i.e. osteoarthrosis of the facets (Pope, 2001). Stabilization of the three-joint complex is assumed to be accompanied by a decrease in LBP, which explains the conflicting and paradoxical reversed connection of disc degeneration and LBP at an advanced age.

Although discography is the gold standard in the diagnosis of discogenic pain, this procedure is invasive and, therefore, not valid for routine diagnostics. Unfortunately, in a chronic LBP patient population no clinical test could differentiate discogenic from non-discogenic pain (Schwarzer et al., 1995). An exception might be the bonyvibration test, in which a small hand-held vibrator is used to produce pain provocation similar to that in discography. This non-invasive pain provocation method can be successfully combined with MRI in identifying symptomatic disc lesions (Yrjämä et al., 1997).

3. Genetic factors in discogenic pain

Significant genetic influence on the susceptibility to LBP has been demonstrated in a cohort study based on the Danish Twin Registry. The study showed that a shared environment is an important component until the age of 15. As people grow older, the effect of a non-shared environment increases and non-additive genetic effects become more evident, indicating an increasing degree of genetic interaction (Hestbaek et al., 2004). Genetic variations in the genes for two of the structural components of the intervertebral disc, collagen IX and aggrecan, have been implicated in disc disease. Gln326Trp in the α2 chain and Arg103Trp in the α3 chain of collagen IX, have been shown to associate with lumbar disc disease (Ala-Kokko, 2002). The latter of these increased the risk of sciatic syndrome 2.5-fold (Paassilta et al., 2001).

Recent studies suggest that LBP is associated with the polymorphisms in the interleukin (IL)1 locus (Solovieva et al., 2004). This is an interesting finding as new evidence suggests that cytokines, especially tumor necrosis factor (TNF)α but probably also IL-1 and IL-6, play an important role in discogenic pain. We genotyped sciatica patients for some inflammatory genes and compared these patients with asymptomatic subjects. A genotype leading to increased production of IL-6 was over-expressed in sciatica patients (Noora Noponen-Hietala, unpublished observation). However, we did not find any evidence for an association between discogenic pain and genetic alterations in IL-1 locus.

4. The role of inflammation and cytokines

Olmarker et al. (1993) showed that nucleus pulposus tissue applied onto spinal nerve roots induced functional, vascular, and morphological abnormalities in the nerve roots. These were often followed by intraradicular fibrosis and neural atrophy. It was also demonstrated that disc cells express TNFα and that topical TNFα caused radicular abnormalities identical to those seen after nucleus pulposus application (Igarashi et al., 2000). Olmarker and Rydevik (2001) showed that selective inhibition of TNFα prevented thrombus formation, intraneural edema and a reduction in porcine nerve root conduction velocity. The promising open-label trial results of anti-TNFα therapy among sciatica

patients also suggest a crucial role for TNFα in lumbar radicular pain (Genevay et al., 2004; Karppinen et al., 2003). However, the preliminary results of a randomized controlled study by Korhonen et al. (unpublished observation) do not unequivocally provide evidence for the use of a single dose of infliximab in the treatment of disc herniation-induced sciatic pain. Further studies are clearly needed to explore anti-TNFα therapy for radicular pain. Before this is completed, off-label use of TNFα-antagonists should be avoided in the treatment of sciatica. In addition to TNF-α, other cytokines may be part of the inflammatory component of radicular pain. Burke et al. (2002) detected increased levels of IL-6 in disc extracts of patients undergoing fusion for discogenic pain. They found additionally increased levels of a chemokine, IL-8. IL-6 is an interesting interleukin as it regulates to a large extent the hepatic acute phase and cachectic responses to an acute inflammatory stimulus (Oldenburg et al., 1993). Recently, it was found that sciatica patients have an elevated acute phase response (Le Gars et al., 2000). Mean sensitized CRP levels were significantly higher in sciatica patients compared with age- and sex-matched controls (1.68 vs. 0.74 mg/l; $P=0.002$).

5. Rationale and outcome of invasive treatments on discogenic pain

A recent Cochrane review showed that surgical discectomy for carefully selected patients with sciatica due to lumbar disc herniation provides faster relief from an acute attack than conservative management, although any positive or negative effects on the lifetime natural history of the underlying disc disease are unclear (Gibson et al., 2004). Additionally, the review also found moderate evidence that percutaneous discectomy produces poorer clinical results than standard discectomy or chymopapain. The less invasive chemonucleolysis was shown to be more effective than a placebo, but less effective than surgical discectomy. No randomized controlled trial (RCT) has been done on laser discectomy.

The biomechanical rationale for the surgical treatment of chronic LBP with suspected instability is to stabilize the symptomatic motion segments in order to eliminate painful motion (Frymoyer et al., 1997). The validity of this treatment concept has been studied lately in RCTs (Fairbank J, 2004; Fritzell et al., 2004) by comparing stabilization with conservative care. The results of the RCTs do not unequivocally support the use of spinal stabilization procedures. Clarifying further the indications of spinal stabilization procedures is clearly needed.

Besides surgery, other less invasive techniques are available for the treatment of discogenic pain. One such novel technique used in LBP and/or sciatica due to disc disruptions is intradiscal electrothermal therapy (IDET), which has been expected to become an alternative to spinal fusion for selected patients. However, the RCTs done so far have yielded contradictory results. Therefore, more basic science and clinical research are needed to illuminate the mechanisms and the value of this potentially beneficial treatment (Biyani et al., 2003). Selective nerve root blocks (SNRB) are used widely for discogenic sciatica. Although there is some indication that repeated SNRBs may prevent surgery (Riew et al., 2000), a recent meta-analysis found only a trend in favor of perineural corticosteroid injections (Paavo Zitting, unpublished observation).

6. Conclusion

Spinal degenerative process starts from the disc at the beginning of the second decade of life. The degeneration process may be coupled with pain at an earlier age, but the connection between disc degeneration and pain is obscured in later life. Genetic, nutritional and mechanical factors play a role in this cascade, but the molecular mechanisms of discogenic pain are largely unknown.

In anti-cytokine therapies efforts are focused on the treatment of the radicular component of discogenic pain. Future therapies may even involve gene therapy, e.g. in non-radiating discogenic pain, though financial evaluations do not favor that trend. Anti-TNF-α therapy seems to be the option with the greatest potential among anti-cytokine treatments, but a great deal of research is needed before its value and potential can be reliably evaluated. Currently it is felt that adequate physical exercise, avoidance of smoking, and the minimization of harmful loads are the only known ways of preventing painful disc disease.

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