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REVIEW ARTICLE

Translational research of herniated discs: current status of diagnosis and treatment

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Abstract Lumbar herniated discs commonly occur in patients 20–40 years of age, and result in acute symptoms of shooting and intractable pain in the low back and/or lower extremities. However, the prognosis of these patients is considered to be very good. Moreover, 70 % of these patients have been reported to be free from sciatica at approximately 6 months after the first onset. Magnetic resonance imaging (MRI) studies have described the spontaneous resorption process of herniated discs, which is a major cause of the reduction of symptoms in patients. New advancements in MRI have recently been developed that have facilitated the examination of nerve tract fibers and identification of symptomatic nerve tissue. Furthermore, the mechanism underlying the resorption process of a herniated disc has been determined. Inflammatory cytokines such as TNF (tumor necrosis factor)-α, angiogenic factors such as vascular endothelial growth factor, and enzymes such as matrix metalloproteinases are intricately related to each other. In our previous studies, matrix metalloproteinase-7 (MMP-7) has been shown to play a crucial role in the initiation of herniated disc resorption. Therefore, we developed recombinant human MMP-7 for intradiscal therapy through an industry–university joint research program. We have already performed in vitro and in vivo experiments to confirm its efficacy; this therapy avoids the side effects associated with surgery, such as nerve tissue damage. Moreover, the phase 1/2 studies of recombinant human (rh) MMP-7 are currently ongoing in the United States, and careful monitoring is required for these clinical trials. In conclusion, patients with lumbar herniated discs may benefit from the development of a less invasive treatment for disc herniation, which can be applied even immediately after the onset of disease symptoms.

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Introduction

Low back pain is the primary reason for patients visiting physicians in Japan. This condition ranks second among the complaints in the United States, following upper respiratory tract complaints [1]. Herniated discs (HD) account for 4 % of the total cases of mechanical low back pain, and occur in approximately 2.8 million patients annually [2]. Patients with lumbar HD experience acute onset unilateral or bilateral lower extremity pain and numbness associated with the low back pain [3]. However, 70 % of lumbar HD patients recover from sciatica within 6 weeks of its onset. Thus, considering the natural history of HD, the overall patient prognosis is good. However, an estimated 10 % of patients will experience continued pain and neurological deficits, and surgical intervention should be considered for these patients [1]. A systematic review comparing surgical intervention and conservative management indicated that surgical intervention enables faster pain relief, compared to prolonged conservative treatment, during short-term follow-up, although no marked differences are noted during long-term follow-up [4, 5].

Lumbar HD patients are primarily between 20 and 40 years of age, employed, and play an active role in

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society. To reduce the quality of life issues caused by surgical intervention, including microdiscectomy, more effective and less invasive treatments—which require less treatment time—need to be developed.

Molecular genetics and biology

Several previous studies have described the potential gene markers for lumbar disc diseases, including collagen 9A2 [6, 7], vitamin D receptor [8], matrix metalloproteinase (MMP)-3 [9], cartilage intermediate layer protein [10], collagen 11A1 [11], thrombospondin (THBS2) [12], sickle tail (SKT) [13], MMP-9 [12], asporin (ASPN) [14], and carbohydrate sulfotransferase [15]. Systematic reviews demonstrated that there is moderate evidence of correlation of ASPN, COLXIA1, SKT, THBS2, and MMP-9 with HD [16]. However, further studies are needed to identify the gene that is strongly correlated with the disease. Assessment of the upregulation and downregulation patterns of specific candidate genes in animal models may facilitate the identification their precise roles in disc degeneration.

Regenerative medicine techniques for the treatment of disc degeneration have recently been developed for clinical use. Co-culture of autologous mesenchymal stem cells with the patient's nucleus pulposus cells or annulus fibrosus cells may be a good alternative for regenerating the degenerated disc matrix [17]. In addition, the administration of autologous platelet-rich plasma may promote a reparative effect on degenerative disc tissues [18]. These methods suggest the potential for regeneration of degenerated disc tissues in the near future.

Development of image examination techniques

The resorption process of HD was demonstrated using sequential magnetic resonance imaging (MRI), and this resorption process may be the reason for the relatively good prognosis in cases of HD (Fig. 1) [19]. Vroomen [20] demonstrated that 70 % of patients with HD indicated the disappearance of sciatica within 6 weeks of its onset. In addition, the non-contained classification types of HD, such as transligamentous extrusion and sequestration, as well as the enhanced contrast noted around HD, indicated a high tendency for resorption, thus suggesting that vascularization around the HD would be an important factor for HD resorption [21]. This HD resorption phenomenon was demonstrated in the lumbar, thoracic, and cervical regions of the spine [22, 23].

A recent study indicated that it was impossible to assess good or unfavorable outcomes using MRI at the 1-year follow-up for patients who had been treated for lumbar HD

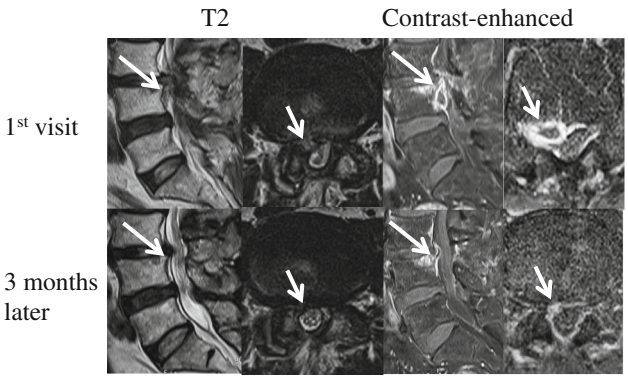

Fig. 1 Sequential magnetic resonance imaging of a 66 year-old man demonstrating resorption of the herniated disc

[24]. However, with recent developments in MRI, the observation of tract fibers with diffusion tensor tract images [25] as well as the identification of symptomatic nerve roots (due to spinal disorders) with diffusion-weighted imaging, is currently possible [26]. Through these new technological advancements in MRI, the identification of symptomatic nerve tissues with HD will be possible in the near future, thus facilitating more accurate investigations for HD patients.

Surgery for HD

A study on HD due to disc rupture or cartilaginous tumor was first reported in 1934. The study concluded that ruptures of the disc were more common than tumors. The authors recommended that the primary mode of treatment should be surgery. In 1939, Love described a surgical technique that involved the identification of an HD mass through myelography and subsequent removal of the HD via partial laminectomy. A study on the long-term outcomes of discectomy, including a follow-up period of more than 10 years, showed relatively favorable results with an average improvement rate of 73.5 % [27]. A prospective randomized multicenter study was performed on 1,244 cases at 13 medical institutes in the United States to compare whether surgical or conservative treatment showed favorable outcomes [28]. When the Short Form 36 and Oswestry Disability Index (ODI) assessment was performed at 3 months, 1 year, and 2 years after intervention, surgical treatment was found to be more effective. However, the findings of that study should be cautiously interpreted, as the crossover rates between the surgery and conservative group were 40 and 45 %, respectively.

The first case of the use of the microendoscopic discectomy system in Japan involved a patient with lumbar HD in 1998. Since then, the use of minimally invasive spinal