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Diffusion-Weighted Magnetic Resonance Tomography in the Diagnosis of Intervertebral Disk Degeneration

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Diffusion-weighted magnetic resonance imaging (DW MRI) is an MRI method providing images of biological tissues weighted for the diffusion of water molecules at the cellular level. Characteristic changes are found in the extent of diffusion of water molecules at the early stages of intervertebral disk degeneration. Dehydration of cell populations in intervertebral disks associated with sharp restriction to diffusion of intra- and extracellular water is reflected as increases in signals on DW MRI scans. Thus, DW MRI is a leading method for the diagnosis of the initial signs of intervertebral disk degeneration, providing for identification of possible indications for neurosurgical intervention.

The human vertebral column has unique structural and physiological characteristics allowing it to support, stabilize, and move our bodies in space throughout life [1, 2]. Impairments to the correct functioning of vertebral structures are generally seen in trauma and degenerative-dystrophic processes and are often apparent clinically as pain and early loss of the ability to work [3, 4]. Despite the active development of instrumented diagnostic methods, the question of the anatomical-physiological conditions for the development of early pathological changes to vertebral column structures remains open. This question has long been a barrier to developing effective treatment methods in this group of patients. New investigation methods addressing the anatomical and physiological conditions underlying the development of vertebral diseases have open up a new view of an old problem.

There is no doubt that T1- and T2-weighted MRI images allow changes in vertebral column structures to be visualized with high levels of precision; they are also highly sensitive for pathological processes [5]. Nonetheless, it is often difficult to distinguish physiological MR signals from MR signals serving as signs of pathological tissue changes, especially in patients with vertebral disease and trauma. The main reason for this is that differences in internal physiological processes between tissues are not always visualized using routine MRI scan protocols [6, 7]. For example, compression fractures of the vertebral bodies have similar characteristics on T1- and T2-weighted images, though in some cases fractures can be due to systemic osteoporosis and in others to metastatic lesions [8].

Current advances in medical science have allowed MRI methods to be modified such that the anatomical and physiological conditions for the development of pathological changes in the vertebral column and particularly intervertebral column degeneration can be detected. DW MRI is among these contemporary diagnostic methods. This technique provides for accurate identification of the extent of diffusion and movement activity of water molecules within cells and the intracellular space, thus visualizing normal tissues and tissues subject to degenerative changes [9, 10]. The DW MRI method was initially actively utilized in the diagnosis of the early signs of ischemic brain lesions, though DW MRI is now among the leading methods for the diagnosis of diseases of the mediastinal, abdominal, and pelvic organs [11]. A relatively new direction is the use of DW MRI to investigate pathological processes in intervertebral disks and the vertebral column in general [12].

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The aim of the present literature review was to analyze current published data on the effectiveness of clinical and research applications of DW MRI in the diagnosis of degenerative change in intervertebral disks. Use of a complex approach to the diagnosis of early signs of intervertebral disk degeneration will provide a deeper understanding of this area and will aid the development of new and effective methods for treating this pathological process.

The Significance of the Diffusion of Water Molecules for Clinical Investigations

Diffusion is a key physiological process consisting of the movement of various substances, including oxygen and carbon dioxide, within cells and in the extracellular space. Diffusion processes support the normal viability of all tissue structures in the body by delivering oxygen and nutrients and carrying metabolic products away [13]. The extent of diffusion depends on the steepness of the gradient between two media. This type of gradient generally arises as a result of a difference in the concentrations of water, proteins, and electrolyte molecules. Diffusion processes also depend on the quantity and density of tissue barriers – cell membranes, collagen fibers, glycosaminoglycan fibers, etc. [14]. The vertebral column includes a variety of tissue barriers, such as collagen fibers, cell membranes, and blood vessels, and there are significant water molecule diffusion gradients between these [15]. For example, adipocytes in subcutaneous fatty tissue are densely appressed to each other and contain small quantities of free water; this means that this tissue has a low extent of diffusion. The cerebrospinal fluid, conversely, contains large amounts of free water and a minimum of tissue barriers to the movement of molecules, leading ultimately to high diffusibility of the fluid [16]. It should be noted that significant changes in the ability of tissues to support diffusion can result from numerous unfavorable factors, among which the dominant are trauma and degenerative diseases. DW MRI, which assesses the ability of tissues to support diffusion, contributes to describing their structural-functional state and the nature of this ability.

The Main Principles of DW MRI

DW MRI is a magnetic resonance tomographic method which yields images of biological tissues weighted for the diffusion of water molecules at the cellular level [17]. The main principle of the operation of DW MRI consists of visualizing and measuring the active movement of molecules in the tissues. DW MRI signal intensity is entirely dependent on diffusion capacity in voxels (three-dimensional pixels) in the study object: the greater the extent of diffusion of water molecules, the more intense the signal on the DW image [18]. Water molecules show two types of movement. "Isotropic diffusion of water" refers to the relatively unrestricted movement of water molecules in all directions. If diffusion is restricted in one or more directions, this type of movement of water molecules is termed anisotropic. Water molecules move within cells, in the extracellular space, and across membranes. In the living body, diffusion of water is not a random process, but follows strict patterns, because of the fact that all tissues are structured. Cell membranes, connective tissue fibers, and nerve cell axons restrict the free movement of water molecules, which divides living tissue into compartments. On the other hand, the physicochemical interactions of water molecules and macromolecules also play a not unimportant role [19].

The contrast of DW images is strictly dependent on the degree of restriction of the free diffusion of water molecules. For example, the movement of water molecules in the gray matter of the brain is essentially isotropic, while diffusion of water in the white matter is anisotropic because of the compact distribution of large numbers of conducting pathways [20]. Pathophysiological processes leading to changes in the permeability of plasma membranes can indirectly produce changes in the diffusion of water molecules. These changes are clearly visualized by DW MRI in terms of the coefficient of diffusion (CD) [21]. Movement of water molecules in the intracellular space is more restricted than that in the extracellular space, because of the presence of large numbers of microbarriers (nuclear membranes, cell organelles). The actions of pathological processes on living tissues produce changes in the ratio of intra- and extracellular fluid in favor of the latter, resulting in restriction to the movement of water molecules. Decreases in the diffusion of water are seen when the viscosity of the medium increases due to high protein content.

DW MRI was initially used only in the diagnosis of neurovascular diseases of the brain. Nonetheless, the essentially similar pathophysiological processes seen in impairments to the cerebral circulation and degenerative diseases of the spine allow this diagnostic method to be used in spinal neurosurgery [22]. Signs such as tissue ischemia and hypoxemia lead to cell membrane depolarization, changes in membrane permeability, and impairments to ion metabolism and the directional flow of water molecules. Cellular edema leads to compression of the extracellular space and, possibly, to impairment of the diffusion of intracellular water due to changes in

organelles. These cellular processes are reflected in DW images as increases in MR signals and low values of CD. Cell lysis and swelling and subsequent tissue degradation lead to sharp increases in the extracellular space and the level of free water, with a simultaneous decrease in the DW MRI signal intensity and an increase in CD.

Each voxel in a DW image has an intensity reflecting the degree of freedom of the diffusion of water molecules in a given location. Using a relative terminology, this means that tissues with anisotropic movement of water molecules will appear brighter, while tissues with isotropic diffusion will be less bright [23]. However, construction of diffusion maps will yield the reverse: low CD values reflect a more restricted degree of diffusion. Thus, the best results are obtained by investigating tissues with predominantly isotropic diffusion (for example, the gray matter of the brain).

Ultrafast image acquisition methods (single short echo pulse, SS EPI) provide significant improvements in the time resolution of DW MRI. The techniques effectively "freeze" movement [24]. Active movement of water molecules within cells are rapidly superimposed because of voluntary and involuntary movements of the patient and pulsation of vessels and CSF. The small contribution of diffusion to proton dephasing is not seen in SS EPI images but is easily be superimposed on T2 effects [24]. It is important to remember that diffusion is a time-dependent process, which means that MR sequences must be run over a period of time for the latter to be observed. Quite long echo times must therefore be manipulated, leading to the use of T2-EPI sequences. High-signal areas retain brightness on DW images, mimicking restriction of the process of diffusion. This phenomenon is known as the T2 glow effect. CD mapping does not have this drawback, so CD values are vital for detecting restricted diffusion [25].

DW MRI in the Diagnosis of Intervertebral Disk Degeneration

The intervertebral disk, as an avascular structure, remains viable only as a result of the diffusional delivery of nutrients and removal of metabolic products. Throughout a human's life, intervertebral disks undergo degenerative processes characterized by dehydration of the nucleus pulposus and the annulus fibrosus [26]. Clinically, these processes are expressed as pain. However, the mechanisms producing pain remain unclear. Only recent studies using DW MRI to address diffusion in normal and degenerative disks have provided a new view of this problem.

Studies on cadaver disks reported by Antoniou et al. showed that decreases in the CD value of the nucleus pulposus are linked with reductions in the quantity of extracellular matrix [27]. At the same time, Beattie et al. studied disks *in vivo* and demonstrated that degenerative disks display a direct relationship between decreased T2 signal intensity and decreased CD [28]. These investigations supported the fact that degenerative disks have low diffusion capacity. The causes of reductions in diffusion of substances through disk tissues remain unclear. However, it can be suggested with a high level of probability that this is partially associated with an increase in the density of the fibrous tissue of the disk. This type of change in disk histoarchitectonics creates multiple microbarriers on the path of fluid movement, subsequently leading to dystrophy and decreased intervertebral disk proteoglycan synthesis [28].

During life, intervertebral disks undergo many morphological and biochemical rearrangements [29]. As noted above, intervertebral disks are essentially avascular structures, where a small cell population is surrounded by an enormous mass of intercellular material. The annulus fibrosis of the disk consists largely of collagen fibers, while most of the nucleus pulposus consists of proteoglycan. Decreases in the level of proteoglycan synthesis are the triggering factor for intervertebral disk degeneration [29, 30]. Replacement of proteoglycan by dense fibrous connective tissue sharply restricts the diffusion of nutrients and water molecules. These processes are regarded as key in the development of disk degeneration [30]. DW MRI provides visualization of these phenomena in disks, at the very earliest stages [31]. CD values directly reflect the microenvironment of diffusing water molecules within cells and in the extracellular space. Thus, CD values are low when dehydration is present and proteoglycan synthesis in the nucleus pulposus is decreased. Many investigations have shown that decreases in CD point to impairments in the structural integrity of intervertebral disks [32]. Thus, measurements of CD in DW MRI allow degenerative processes in disks to be confirmed at the early stages of their development, when they are still not visible on routine T2-weighted images. Figure 1 shows an MRI map of an intervertebral disk with degenerative change acquired using different regimes (T1, T2, and DW regimes).

Conclusions

DW MRI is a contemporary method for the instrumented diagnosis of many diseases of the vertebral column, particularly degenerative processes in vertebral disks. The potential for non-invasive *in vivo* assessment of

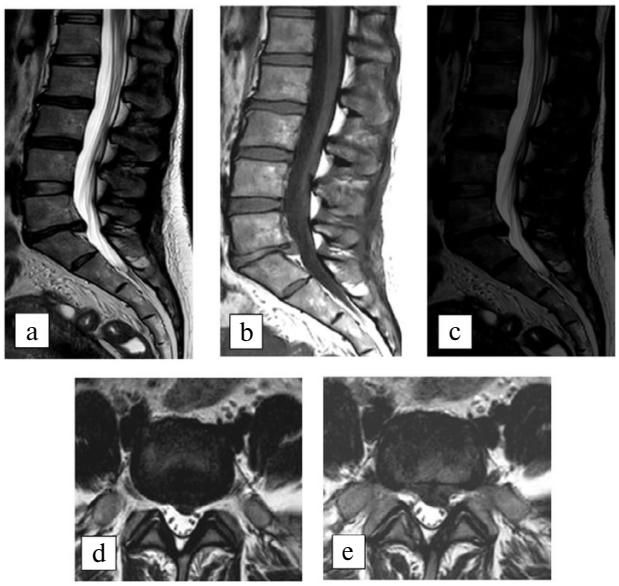

Fig. 1. MRI scan images of the lumbosacral segment of the spine: a) sagittal MR tomogram, T2 regime; b) sagittal MR tomogram, T1 regime; c) sagittal MR tomogram, DW MRI regime; d) axial MR tomogram, T2 regime; e) axial MR tomogram, DW MRI regime.

such important physiological processes as diffusion of water molecules deepens our understanding of the molecular mechanisms of disk degeneration. Nonetheless, wide use of DW MRI in clinical practice requires several problems relating to conducting the investigations to be solved. It is widely known that the quality of DW images depends on the movements of the object under study: the more the patient performs voluntary and involuntary movements, the lower the quality of the image, so particular attention must be paid to minimizing movements made by the patient. The high cost of this study method and the limited access to it also hinder its wide clinical application. On the other hand, the continuing development of new technologies, including rapid scanning of DW images, significantly decreases patient investigation duration, decreasing the cost of the investigation and making DW MRI accessible to larger numbers of patients. Thus, the DW MRI method will shortly occupy a firm place as the leading instrumented method for the diagnosis of degenerative processes in the vertebral column overall and intervertebral disks in particular. The ability to visualize the main pathophysiological processes playing key roles in the pathogenesis of disk degeneration will widen our knowledge of the pathogenesis of this state and, on this basis, promote the development of new biological therapeutic methods.

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