THE ROLE OF INFECTIOUS PATHOGENS IN ETIOPATHOGENESIS OF DEGENERATIVE INTERVERTEBRAL DISC

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Objective. To analyze the presence of infectious pathogens in the intervertebral disc tissues as possible pathogenetic factor in the development of degenerative diseases of the spine.

Material and Method. In 2017–2018, a prospective exploratory research was conducted, which included 64 patients with degenerative disease of the spine who met the following inclusion criteria: the presence of clinically and instrumentally proven hernias of the intervertebral discs in the lumbosacral spine, the absence of a history of surgical interventions on the spine, non-intake of antibacterial drugs for the year before surgery, and Modic I and/or II type changes on MRI. All patients underwent interventions with sampling of intervertebral disc material; a total of 80 discs were examined. The obtained materials were subjected to microbiological and histopathological studies.

Results. Out of 64 patients, only 1 (1.6 %) revealed the presence of bacterial flora in the intervertebral disc tissue (*Propionibacterium acnes* strain). It can be assumed that the identified bacterial flora is the result of contamination. It is also possible that the infectious agent joined already during the development of degenerative disease of the spine. If the bacterial flora was a pathogenetic factor, then it can be assumed that the pathogenesis of the disease is polyetiological and includes the infectious process as a rare event.

Conclusions. Given the high interest of specialists in the pathogenesis of degenerative diseases, it seems appropriate to conduct further studies in this direction using various laboratory diagnostic methods with high sensitivity and specificity.

Key Words: spine, disc herniation, intervertebral disc herniation, microdiscectomy, degenerative disease, bacteria, infection.

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Degenerative diseases of the lumbar spine are an alarming problem of modern medicine. According to current estimates, up to 80–90 % of the population experience spinal pain [1]. The number of people with spine-related disability in the World increased from 58.2 million in 1990 to 83.0 million in 2010 [2]. However, although degenerative spinal diseases are of high prevalence and socio-economic importance, there is still no consensus on their etiology and pathogenesis. According to the existing theories, the pathogenesis of degenerative diseases of the spine (e.g., osteochondrosis) is multifactorial and associated with the following risk factors: age-related involutional changes in the body; mechanical, immune, traumatic, vascular, infectious, hormonal, functional, and hereditary factors; age; smoking; and heavy physical labor [3, 4].

The first research on the association between degenerative diseases and infectious pathogens was the study by Stirling et al. [5], which was published in the Lancet journal in 2001. The study revealed the presence of anaerobic gram-positive microorganisms in the intervertebral disc tissue in 53 % of patients with sciatica, with 84 % of them being presented by *Propionibacterium acnes (P. acnes)*. Afterwards, there were also some other works on this issue published in foreign journals. However, this topic remains poorly explored in the domestic literature, which prompted us to initiate this study.

The aim of the study is to analyze the presence of infectious pathogens in the intervertebral disc tissues as a possible pathogenetic factor in the development of degenerative diseases of the spine.

Material and Methods

A prospective exploratory study was conducted at the Department of Traumatology, Orthopedics and Spine Surgery, Petrovsky Russian Research Center of Surgery (Moscow) in the period of October 2017 to October 2018. The study was aimed to detect infectious pathogens in intervertebral disc tissues and assess their role in the pathogenesis of degenerative diseases of the spine.

The study included 64 patients aged 18 years and older suffering from clinically and instrumentally verified degenerative diseases of the lumbosacral spine and meeting the inclusion criteria. There were 29 (45.3 %) women (median age, 46.4 years) and 35 (54.7 %) men (median age, 46.8 years) among the patients.

The inclusion criteria were as follows: clinically and instrumentally verified hernias of intervertebral discs in the lumbosacral spine, no history of spine surgery, no history of antibacterial drug consumption for a year prior to surgery, and Modic type I and/or II changes.

Patients included in the study underwent surgery for degenerative diseases, namely intervertebral disc hernias; disc tissue samples were collected for microbiological and histological examination.

Surgery for lumbar disc herniation included Caspar microsurgical discecto-

my; stabilization of the affected segment using rigid or dynamic fixation systems was conducted based on the indications. Interventions were performed by the same team of surgeons in the same operating room in compliance with aseptic and antiseptic techniques for preoperative prevention of infectious complications (intravenous injection of 2.0 g of cefazolin one hour before skin incision; in case of intolerance to cefazolin, it was replaced with another drug upon consultation with the clinical pharmacologist).

The most prevalent segment affected in the studied patients was L4–L5 (24 cases, 37.5 %); L5–S1 herniation was a little less common (21 cases, 32.8 %), while L3–L4 segment changes were noted in 3 patients (4.7 %). The study also included 16 (25.0 %) patients with two-level degenerative disc diseases. Samples of 80 intervertebral discs were collected in total.

Microbiological analysis included isolation and identification of the detected microorganism. Clinical samples were taken in full compliance with regulations using transportation systems (Copan, Italy). The obtained samples were seeded in general purpose media and selective solid MAST media (MAST Group Ltd., United Kingdom) according to the standard methods. The samples were cultivated under aerobic and anaerobic conditions (using the BD GasPak™ system, USA); identification of the isolated microorganism was carried out using a microbiological testing system (VITEK® 2 Compact Biomerieux, France).

For histopathological analysis, intervertebral disc samples were dissected into 0.4–0.5-cm fragments. The specimen were fixed in 10 % neutral buffered formalin for 12–24 hrs according to the standard technique and then embedded in paraffin. Deparaffinized 3–4-μm thick sections were stained with hematoxylin-eosin, van Gieson's picrofuchsin, Heidenhain's azan, and orcein. Histochemical methods, namely staining with periodic acid-Schiff and toluidine blue, were used to study the properties of the extracellular matrix. The von Kossa technique was used to detect the presence of calcium deposits. The samples were analyzed by transmission electronic microscopy using a Leica DM1000 LED light microscope in order to detect bacterial biofilms in the intervertebral discs.

All patients underwent examination by MRI and radiography in the preoperative period. MRI data on changes in the bone marrow and adjacent vertebral endplates were evaluated according to the Modic classification system [6]. Radiographic examination was used to assess segmental mobility and degenerative changes in the facet joints and endplates.

The study followed ethical principles in accordance with the Helsinki Declaration of 1964 [7]. All patients provided written informed consent for diagnostic testing and medical intervention.

The data were analyzed by bacteriologists, clinical pharmacologists, and pathologists. The data were subjected to statistical analysis.

Results

Analysis of the intervertebral disc samples of 64 patients (80 discs in total) with degenerative diseases of the lumbar spine suffering from radicular syndrome and back pain due to disc herniation revealed the presence of bacterial flora *(P. acnes)* in only one (1.6 %) case. Samples of the remaining patients were free of bacterial flora; histological examination revealed no signs of inflammation (only the signs of degenerative changes).

The pathological strain was detected in a 28-year-old patient with L4–L5 disc herniation and sequestration. The patient had a concomitant diagnosis of class II obesity (body mass index, 37.2 kg/m^2). A microbiological analysis revealed anaerobic gram-positive bacteria identified as *P. acnes*. Histological examination demonstrated small foci of edema and fresh hemorrhages (Fig. 1), dystrophic uneven changes in chondrocytes and intercellular substance, foci of calcification, as well as signs of regenerative changes in chondrocytes (Fig. 2).

The patient received antibacterial prophylaxis according to the protocols for microsurgical discectomy (cefazolin, 2.0 g i.v. before surgery). Radicular syndrome stabilized; back pain disappeared within 6 weeks after surgery. The patient had no complaints at 6-month and 12-month follow-up.

Discussion

The theory of infectious etiology of degenerative diseases of the intervertebral discs was first proposed by a group of British scientists in 2001. The authors stated that low-virulent microorganisms, in particular *P. acnes*, can cause a chronic low-grade infection in lumbar intervertebral discs of the patients with sciatica [5]. In this study, anaerobic gram-positive microorganisms were found in 53 % of patients with sciatica, with 84 % of the cases represented by *P. acnes*. According to the specialists, other microorganisms besides *P. acnes* were also revealed: *S. aureus, C. propinquum, C. freundii,* and *B. cereus* [2].

According to epidemiological studies, the prevalence of *P. acnes* ranges from 13 % to 44 %. Furthermore, many authors consider the presence of this pathogen in the intervertebral disc tissue one of the risk factors for Modic changes, nonspecific back pain, and sciatica [8–10]. The most pronounced symptoms are observed in Modic type I changes [11]. Moreover, this microorganism takes the second place in the incidence of infectious diseases of the shoulder joint, the third place among the causes of periprosthetic infections; it is also often associated with vertebral osteomyelitis, purulent discitis, and spondylodiscitis [11, 12].

To date, there is no unified standard system for diagnosing infectious and degenerative diseases of the spine. Having analyzed the literature data, a research group formed a system based on a combination of histopathological criteria: the presence of granulation tissue, chronic inflammatory cells, neutrophilia, and dense fibrotic foci [13].

A meta-analysis of nine studies (602 patients) showed that six of them favored the infectious hypothesis (microorganisms were found on average in 45.2 % of the patients in these studies), with *P. acnes* being more common (59.2 %) in patients with disc her-

niation [14]. According to another meta-analysis, microorganisms were detected in nine of the 11 studies analyzed, while infection was found on average in 34 % of patients, with *P. acnes* being the most common microorganism: it was identified in 45 % of the positive samples. We also detected the *P. acnes* strain in our study; however, the bacteria was found only in one out of 64 patients. A correlation between the presence of bacteria in the intervertebral disc tissues and back pain, Modic I changes, and disc herniation was noted [15]. An analysis of 404 patients from eight different studies revealed 132 (32.7 %) cases of intervertebral disc infection, with the same microorganism, *P. acnes*, being the most common pathogen (68.9 %) [2].

Patients suffering from lower back pain were divided into two groups for comparison: individuals receiving antibacterial therapy and patients receiving placebo. A statistically significant improvement in all parameters (MRI signs, pain intensity in the lower back and lower extremities) was noted in the first group [16]. Similar data were obtained by researchers from Denmark and Great Britain: back pain was shown to be associated with edematous endplates and swollen bone marrow of the vertebral bodies adjacent to the damaged disc, which might be caused by low-virulent anaerobic bacteria [16]. According to a series of studies, antibacterial treatment of non-specific back pain is more effective than placebo therapy [16, 17]. A multicenter, randomized, blind study of the feasibility of prescribing antibacterial drugs to treat back pain is currently ongoing [18]. In our study, only standard antibacterial prophylaxis was carried out; no antibacterial therapy was used, since there was no evidence for the infectious origin of the disease.

The well-known DISC study of an Australian cohort of 168 individuals (84 women and 84 men) revealed a pathogen in the intervertebral discs in 19.6 % of the patients (50 % of the cases were represented by *P. acnes*) [19]. The authors allocated the patients into several groups based on the area of surgical intervention: 27.8 % of the cases underwent lumbar fusions, and 18.5 % had cervical operations. However, the researchers noted clinical insignificance of the data and indicated the need for a multicenter study using a proper sample.

A group of researchers [20] conducted a genetic analysis of 15 herniated intervertebral discs, five degenerative discs, and two healthy discs. All the three disc groups varied in the number of the proteins involved in the immune response

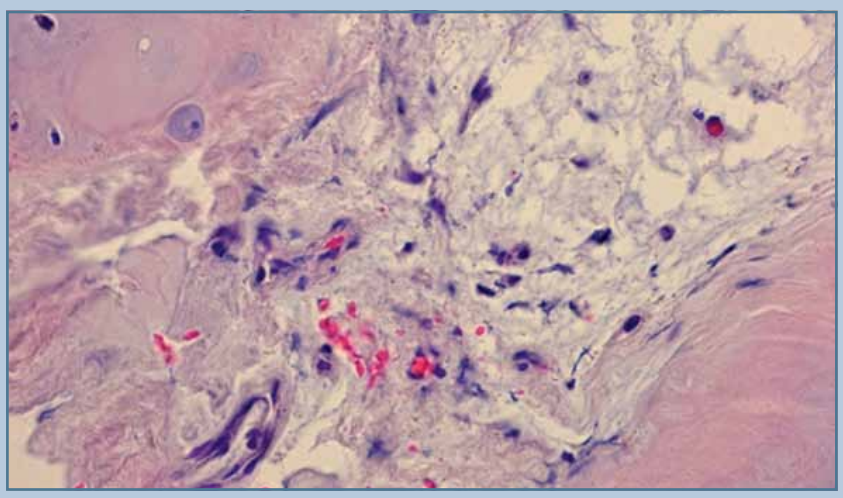

Fig. 1
Foci of edema and sclerosis are observed in the sequestrated areas of cartilage; chondrocytes are sparse, with dystrophic changes seen in most of them; some chondrocytes are in a state of necrobiosis and necrosis; staining with hematoxylin and eosin; ×400 magnification

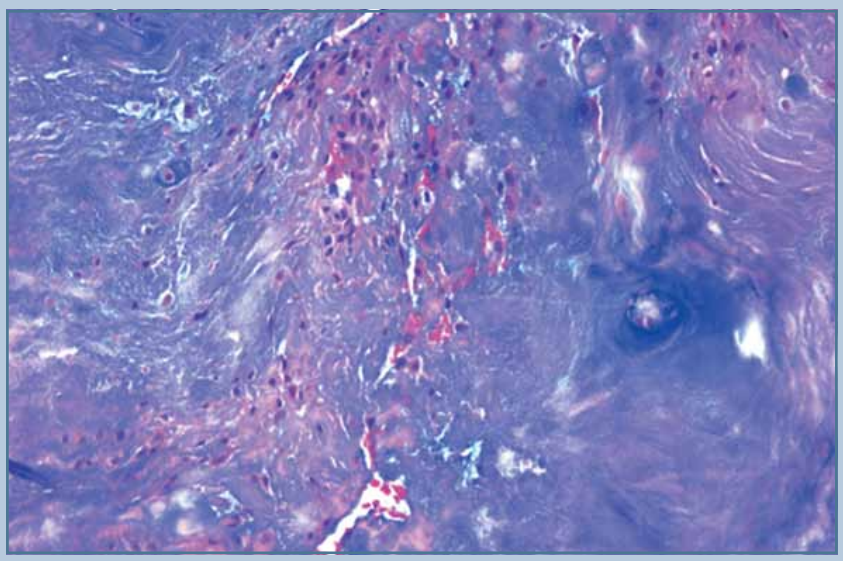

Fig. 2
Unevenly metachromatic ground substance, areas of vascularization surrounded by foci of chronic inflammation comprised of lymphocytes and histiocytic elements in the sequestered intervertebral disc tissue; staining with azan; ×200 magnification

during the infectious process (lysozyme, defensin, dermcidin, cathepsin G, phospholipase A2, ubiquitin C): one group had the largest number of these proteins, the second group had slightly smaller number of the proteins, while the third group had the smallest number of the proteins among the other groups.

Specialists from China [21] examined 46 patients with hernias. The authors studied disc samples and paravertebral muscles using PCR. No microbial genes were found in the muscle tissue. However, a bacterial gene was found in the intervertebral disc samples in 23.9 % of cases, which made the authors suggest a low probability of sample contamination and a likely presence of an infectious pathogen.

Analysis of the surgical samples of 290 patients obtained during microdiscectomy and biopsy of the intervertebral disc tissue revealed *Propionibacterium* species in 40 % of cases, staphylococci in 11 % of patients, and alpha-hemolytic streptococci in 3 % of individuals. The authors [22] suggested the involvement of *P. acnes* in the pathogenesis of intervertebral disc degeneration. A similar study was conducted using samples of 368 patients obtained during microsurgical discectomy. Bacteria were detected in 162 (44 %) individuals, including 119 (32.3 %) cases of *P. acnes. P. acnes* was cultured exclusively in 89 patients and in combination with other microorganisms (mainly *Staphylococcus*) in 30 cases. This study confirms the predominance of *P. acnes* in the tissues of herniated discs. Moreover, it provides the first visual evidence of the presence of bacterial biofilms (which have not been detected in our study) thus indicating an infection rather than sample contamination [23].

Analysis of the treatment of 83 patients revealed the presence of microorganisms in 40 (48 %) cases, with 43 cases being bacterial-free. Based on the obtained results and having taken into account the presence of multinucleated cells, low correlation with previous discography, and the absence of postoperative infectious inflammation, the authors [24] suggested the involvement of low-grade spondylodiscitis in degenerative changes in the intervertebral discs. *P. acnes* strain was detected in 28 cases, coagulase-negative staphylococci were observed in 16 patients. Interestingly, that the majority of the infected intervertebral discs was found in men. The most contaminated segment was L4–L5. No correlation between the presence of an infectious agent and Modic changes was revealed. We also evaluated Modic changes in our study. There were also no signs indicating the presence of infection in the intervertebral discs. A group of American researchers analyzed 169 discs obtained from 87 patients: 76 (45 %) were found to be infected, with *P. acnes* and staphylococci strains being detected in 34 and 30 disc samples, respectively. According to the authors [25], local bacterial biofilms are directly associated with disc hernias and discogenic back pain.

A group of French researchers [26] detected *P. acnes* in only 2 (3.7 %) out of 54 intervertebral discs, which coincides with the results of our study. Control samples of the ligamentum flavum obtained from the same patients were also contaminated with bacteria. Similar control studies yielded a positive result in 10 (18.5 %) cases. Air samples from the operating room and laminar flow were also examined: *P. acnes* was detected in three and four cases, respectively. The authors [26] considered sample contamination to be the most likely explanation to the occurrence of microorganisms. The data are consistent with other studies, in which *P. acnes* strain was found in 21.5 % of tissue samples and 16.5 % of surgical wound lavage obtained during spinal surgery.

There is also a theory of the involvement of an infectious agent in the pathogenesis of sciatica. Israeli researchers [27] analyzed 120 samples obtained from 30 patients. A total of 116 samples turned out to be sterile; growth of anaerobic bacteria (coagulase-negative staphylococci) was recorded in 4 cases (2 patients). The authors believe that the results obtained deny the infectious etiology of sciatica. It is possible that microflora growth described in the previous studies can be partially due to intraoperative contamination, which the researchers try to avoid by following the most stringent aseptic and antiseptic techniques [27]. According to the recommendations and protocols, observance of the rules of aseptic and antiseptic surgery are the same in different parts of the World. Apparently, even slight deviations or disregard of rules result in sample contamination.

In order to reproduce and analyze the infection observed in the intervertebral discs, specialists conduct experiments in laboratory conditions. Chen et al. [28] administered *P. acnes* and *S. aureus* into the discs of rabbits and performed histological analysis of the disc samples. *P. acnes* was found to induce degenerative changes in the intervertebral discs, endplate damage, and Modic type I changes. *S. aureus* caused discitis with severe consequences (including death). A group of American specialists conducted quite an interesting study. *P. acnes* was isolated under aseptic conditions from the L4–L5 disc of a patient with back pain and Modic type I changes' after which this biological material was injected into the caudal intervertebral discs of laboratory rats. Proliferation of *P. acnes*, as well as activation of IL-1 and IL-6 were noted on day 3. On day 7, disc degeneration in the form of fibrotic changes in the endplates was observed; TNF-α activity increased in the areas of endplate damage, cell infiltration was noted; the bone marrow remained intact. On day 14, endplates and the trabecular bone adjacent to the disc space were resorbed almost completely, fibrous tissues can be traced to the bone marrow. The highest activity levels of T cells and TNF-α were detected at the border of the disc substance and bone marrow; Modic type I changes were observed. The authors concluded that *P. acnes* bacteria proliferate in the disc sample causing degenerative changes in bone marrow classified as Modic type I changes. Another group of researchers [30] inoculated *P. acnes* culture into the L3–L4 and L4–L5 discs of a rabbit; L2–L3 discs were injected with 100 mL of physiological saline; L5–L6 discs were left intact. The authors showed that *P. acnes* can cause degenerative disc changes and an inflammatory response in endplates,

which were classified as time-dependent Modic type I or II changes. *P. acnes* bacteria accumulate in the endplate region, which provides the most favorable condition for their growth. There, the microorganism causes low-grade inflammation by attracting immune cells resulting in MRI signal changes (Modic changes). In the conclusion section, the authors pointed out the relationship between degenerative changes in the spine, back pain and Modic changes. These changes, in turn, are associated with the presence of *P. acnes* in the conjunction area of the disc and the subchondral bone [31].

Considering the prevalence of this theory among specialists, there are numerous disputes about the way of microbial contamination of the intervertebral discs. Possible contamination mechanisms include bacteremia, translocation of bacteria through the intestinal wall, as well as morphological features of the nucleus pulposus (these tissues provide extremely favorable conditions for proliferation of microorganisms due to the absence of vascularization) [19]. *P. acnes* can be present in the bloodstream in small amounts; however, the non-vascular structure of the nucleus pulposus can provide an ideal environment for the proliferation of opportunistic microorganisms [32]. Endplate cartilage damage as a result of degeneration additionally facilitates inflammatory and infectious complications due to the increased cartilage permeability [33].

Retrograde bacterial migration from the pelvis is also possible. In 1967, Batson described the epidural venous plexus (which was subsequently called Batson venous plexus or Batson veins), which collects venous blood from all vertebral bodies and connects it with the pelvic venous system. Due to valvular insufficiency, when the intra-abdominal pressure rises to its maximum, retrograde spread of the infection from the pelvic organs can occur. This feature can explain the frequent comorbidity of spondylodiscitis with inflammatory diseases of the genitourinary tract and organs of the abdominal cavity. However, the mechanism remains debatable [24].

Conclusion

No convincing data on the involvement of microorganisms in degenerative diseases of the lumbosacral spine have been obtained. Of 64 cases, only one (1.6 %) patient had bacterial flora (*Propionibacterium acnes*). The presence of pathogenic bacteria in the disc sample can be due to contamination. However, the possible involvement of the microorganism in the development of the disease cannot be excluded completely. If the bacterial flora was a pathogenetic factor in this case, it is logical to assume that pathogenesis of degenerative changes in the intervertebral discs is multifactorial and can also include infection (in rare cases).

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