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ORIGINAL ARTICLE

Prospective study using anterior approach did not show association between Modic 1 changes and low grade infection in lumbar spine

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Abstract
Introduction The modern literature is producing a rapidly growing number of articles which highlight the relationship between infection and lumbar disc degeneration. However, the means by which samples are collected is questionable. Posterior approach surgery is not free from skin contamination. The possibility of intraoperative contamination of disc biopsies cannot be excluded.
Objective The objective of this study was to determine if an association existed between lumbar disc degeneration and chronic infection of the intervertebral disc.
Materials and methods 313 patients (186/127, F/M) with chronic low back pain secondary to degenerative disc disease which was resistant to medical treatment were included in a single-centre prospective study. All underwent a lumbar anterior video-assisted minimally invasive fusion or disc prosthesis in L4–L5 and/or L5–S1 via an anterior retroperitoneal approach. The patients MRI scans demonstrated in Pfirrmann's classification grade IV or V disc degeneration; 385 disc drives were taken. In terms of Modic changes, 303 Modic 1, 58 Modic II and 24 absence of Modic change, respectively. All underwent intraoperative biopsy, performed according to a strict aseptic protocol. The biopsies were then cultured for 4 weeks with specialised enrichment cultures and subjected to histopathological analysis.
Results The mean age was 47 ± 8.6 years sterile cultures were obtained in 379 samples (98.4 %) and 6 were positive (1.6 %). The cultured bacteria were: *Propionibacterium acnes* (*n*:2), *Staphylococcus epidermidis* (*n*:2), *Citrobacter freundii* (*n*:1), and *Saccharopolyspora hirsuta* (*n*:1). Histopathological analysis did not demonstrate any evidence of a neutrophilia. There were no delayed or secondary infections.
Discussion and conclusion Unlike the posterior approach where contamination is common, the anterior video-assisted approach allows a biopsy without skin contact. This approach to the spine is the most effective way to eliminate the risk of contamination. Our results confirm the absence of any relationship between infection and disc degeneration. We suggest that the 6 positive samples in our study may be related to contamination. The absence of infection at 1-year followup is an additional argument in favour of our results. In conclusion, our study shows no association between infection and disc degeneration. The pathophysiology of disc degeneration is complex, but the current literature opens new perspectives.

Keywords *Propionibacterium acnes* · Modic 1 · Low back pain · Infection · Disc degeneration

Introduction

In the US, 60–80 % of the population will complain of chronic back pain at some time in their lives. This is the third most common reason for chronic disability and the median age for patients at presentation is 45. Its economic cost is estimated between 50 and 100 billion dollars per year [1]. In France, the High Committee on Public Health estimates that 52 visits in 1000 general practitioners relate to spinal disease, 36 of these are related to disc pathology. In 2004, the prevalence of chronic low back pain was 7.9 % for men and 7.5 % for women [2]. While chronic

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back pain is the result of many factors, the main cause is degenerative disc disease [3–6]. It has long been suggested that this resulted from an increase in intradiscal pressure due to excessive loads exceeding the biomechanical resilience of the disc. It is now accepted that mechanical stresses alone are insufficient [7]. Risk factors such as age, gender, posture, vibration, smoking, obesity, activity and occupation are now well recognised as aetiological factors [8]. Environmental factors have a much less important role [9] and the possibility of an infectious origin has now been presented in the literature for many years [10–13]. The last danish paper proposing long antibiotic treatment for low back pain induced a lot of debates [14].

The objective of this work is to determine if an association existed between lumbar disc degeneration and chronic infection of the intervertebral disc. This work is important because new information allows us to explore alternative therapeutic solutions and to develop new prophylactic and diagnostic tests of disc degeneration.

Materials and methods

This was a prospective continuous cohort of 313 patients suffering from disabling chronic low back pain which was resistant to medical treatment for more than 1 year. We excluded spinal tumours, infections and trauma from the study. This series included 186 men and 127 women with a mean age was 46.4 ± 8.9 years. The patients underwent MRI and radiographs as part of the preoperative assessment, disc degeneration was evaluated according to the classification of Pfirrmann [15] and Modic [16]. Evaluation was performed by an independent radiologist and an orthopaedic surgeon who was not involved in the study. No intraobserver evaluation was done.

197 patients (63 %) received injection therapy (epidural and facet). All patients were operated between 1/11/07 and 01/01/14. Patients were treated in different centres and referred to us due to persistant LBP. Epidural injections are not common in our practice but were reported to be exhaustive in the clinical history.

They underwent a lumbar anterior retroperitoneal video-assisted approach to permit ALIF or disc arthroplasty at L4–L5 and/or L5–S1 levels [17]. Some patients underwent surgery on multiple discs. Three hundred and eighty-five disc biopsies were taken. The surgery is performed in "the French-position" [18]. After positioning of retractors to allow the disc to be visualised the level is checked on the image intensifier.

The samples are taken using the protocol approved by the bacteriology department of our institution, with single-use instruments and who have not been in contact with the rest of the instrumentation. The method is strictly aseptic to avoid incidental contamination (Fig. 1).

The first sample is sent to the bacteriology laboratory and the second is sent to pathology. Bacteriological analysis was performed according to a reproducible protocol. The disc fragments were cultured in a Brain-Heart type culture medium (blood, PolyViteX® and Schaedler) and then placed in ovens at 37 °C enriched with 5 % CO_2 for 15 days to promote the proliferation of anaerobic bacteria. After this initial incubation period, macroscopic analysis assessed the presence of bacterial colonies. These colonies were then subjected to a semi- quantitative analysis, microscopic identification and culture and sensitivity.

Histological analysis was carried out with a reproducible protocol. The sample is set in 10 % buffered formalin and embedded in paraffin using a process of automatic dehydration. Cuts are performed by a microtome. After standard processing with HES (Hematein—eosin—Safran) the sample can be presented for analysis by a pathologist.

The patients were reviewed in the usual fashion following lumbar spine fusion surgery. They all received a pre-operative visit and follow-up at 1, 3 and 6 months and annually thereafter. During these consultations, the clinical and functional scores were recorded (weight, height, EVA, SF-36, Oswestry). Statistical analysis was performed with SPSS IBM software (version 20; SPSS Inc., Chicago, IL, USA).

Results

In total, 385 samples of the intervertebral disc of 313 patients were examined. The mean age of the study patients was 47.6 months ± 13. All patients were immunocompetent.

Preoperative MRI study demonstrated Modic I changes in 303 cases (78.7 %), Modic II in 58 cases (15.1 %), and the absence of Modic change in 24 cases (6.2 %). According to Pfirrmann classification we had 50 grade 2, 211 grade 3 and 124 grade 4.

We highlighted six positive samples of 385 (1.6 %). The other 379 samples had sterile cultures (98.4 %). Bacteria found in these six samples were: 2 *Propionibacterium acnes* (33 %), *Staphylococcus epidermidis* 2 (33 %), 1 *Citrobacter freundii* (17 %), and *Saccharopolyspora hirsuta* 1 (17 %). Of the 6 patients with a positive culture, 5 patients had Modic I changes and one patient had type II Modic changes.

Of the 385 biopsies performed at the intervertebral disc 123 biopsies were on the L4–L5 disc (32 %), and 262 of the L5–S1 level (68 %). The six positive samples originated from L5 to S1 disc biopsies.

In two patients with a positive culture for the L5–S1 disc biopsy for the L4–L5 disc surgery at the same time returned negative cultures.

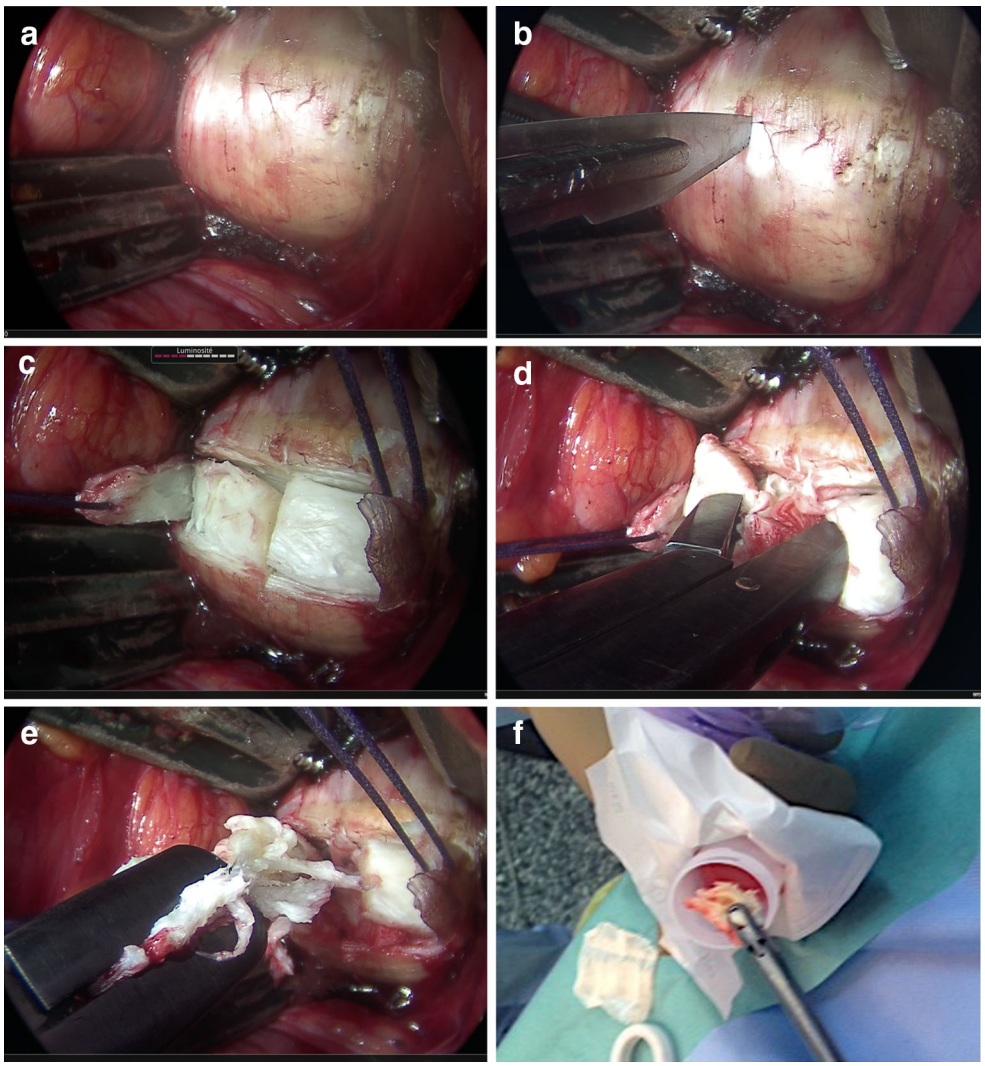

Fig. 1 Illustrations of the sampling procedure. **a** disc exposure. **b** disc opening. **c** disc open with sterile single use instruments. **d** harvesting of the anterior part of the nucleus. **e** harvesting of the interior part of the disc. **f** direct conservation of the sample and transmission to the lab

Table 1 Population's characteristics

	Height (cm)	Weight (kg)	BMI (kg/cm^2)	VAS back pain (mm)	VAS leg pain (mm)	Oswestry score (%)	SF-36 PCS	SF36 MCS
Mean	169	68	23.6	6.9	3	44	29.9	38.3
SEM	17	12	3.2	1.1	2.2	12	3.8	7.6

The results of the histological examination of the discs concluded a "histological appearance of nonspecific fibrous remodelling of the intervertebral disc." It found no features suggestive of a acute inflammatory response, in particular, there was no evidence of neutrophils within the sample. The histological appearance was similar to that of a fibrocartilage tissue.

Postoperative systematic monitoring of 313 patients has not demonstrated any secondary infections (Table 1).

Discussion

The appearance of Modic I changes on MRI is associated with chronic low back pain [19]. However, the reason for the appearance of this inflammation at the endplates is unclear. Different hypotheses have been proposed including mechanical causes. We now know that the mechanical stresses are insufficient in disc degeneration [7].

The recent literature has introduced the idea that an infection of the intervertebral disc can cause herniation and possibly sciatica [12, 13]. The bacterium demonstrated was *P. acnes*. It was obtained by prolonged culturing. The samples were positive in 16 cases out of 140 (11.4 %). However, the possibility of contamination of samples is high; patients received epidural injections [10, 20] and the posterior approach is at high risk of contamination. In a recent paper, the pejorative effect of *P. acnes* on disc height was described as well as the association with annular tear [21].

Studies have also revealed the presence of bacteria in the intervertebral disc. Some found infection in nearly 48 % of samples [22]. The possibility of contamination cannot be ruled out as mixed microbial flora were recovered in 25 % of cases.

Recently, a group of international researchers suggested an association between herniated discs and the presence of *P. acnes* [23]. They published a study demonstrating clinical and radiological improvement of chronic low back pain treated with antibiotics [24]. The media and the scientific community have responded with interest. The implications of this study are obviously important.

The vascularization of the disc is associated with disc degeneration as shown by Freemont [25] and this could be a reason for antibiotic efficacy. It is also well known that spondylodiscitis can occur even in young adult but it has never been demonstrated that systemic spread of the antibiotic is well distributed in disc material.

The authors did not conduct pre and post-treatment samples allowing no microbiological confirmation, the distribution of the cohorts demonstrates a selection bias, the anti-inflammatory effect of the antibiotics, however low, is not quantified. Finally the study supports the presence of an inflammatory or infectious process, but no biological examination was performed (C-reactive protein or interleukin-6). These criticisms make the interpretation of this study difficult [26].

While these studies have considered the presence of a low-grade infection, numerous studies have established the corollary. The authors show no association between the phenomena of disc degeneration and the presence of a low-grade infection [27].

Contamination of different samples by *P. acnes* is frequent [28]. This is a widespread commensal organism of humans with the potential to cause contamination of disc biopsies obtained via a posterior approach where vicinity of the skin is very close during minimal invasive or microsurgical exposure. This biopsies resulting in many false positives [29].

Faced with these contradictions, our series is a large cohort prospective study to establish conclusive results. We decided to differentiate ourselves from other studies and favoured the anterior spine as a site from which to take biopsies. Apart from the advantages of this technique, the anterior retroperitoneal approach is the most effective approach to eliminate skin contact and the subsequent risk of contamination [17].

Our results highlight the lack of low-grade infection in pathological discs. The six positive samples (1.6 %) can reasonably be associated with contamination and do not represent the presence of in situ infection. The absence of histological evidence of an inflammatory response and also early or late surgical site infection is an argument in favour of our results. The administration of an epidural or facet injection does not increase the risk of contamination of the disc.

It is clear that there is an inflammatory component involved in disc degeneration is established, the origin of this is uncertain. Some authors consider that this inflammation is caused by the presence of bacterial [12, 23, 24] or viral pathogens [30]. From our study, we demonstrate that this is not the case. In fact, recent studies of twins identified an important genetic origin to in 74 % of cases [31, 32]. Genetic analysis of cytokines [interleukins, TNF (tumor necrosis factor), IGF (insulin-like growth factor)] shows that the risk of disc degeneration was 3 times higher in patients carrying specific polymorphisms [33–36]. Thus, the presence of a polymorphism induces overexpression of catalysing enzymes which degrade discs by triggering the inflammatory cascade.

Currently, the search for genetic risk factors produces a rapidly increasing number of articles but, like any complex disease, genetic associations found in disc degeneration are difficult to validate [37]. Functional genomics will allow us in the near future to answer the origin of inflammation in disc degeneration. In an editorial, Max Aebi [38] recently pointed out that many patients with low back pain, Modic 1 changes and disc herniation have no evidence of infection and it is difficult to treat them with antibiotics without any proof. More specific imaging techniques using markers of infection are requested for further researches.

Conclusion

Despite the media coverage of recent studies, disc degeneration is a complex phenomenon. The understanding of inflammation causing chronic back pain extends beyond the bacterial or viral infections. Our study, a large cohort, fails to establish that the inflammation related to disc degeneration is caused by bacteria.

Currently, improving scientific techniques lead to the discovery of new factors which contribute to the understanding of biological mediators, biochemical and genetic mechanisms.

Genetic perspectives are of considerable importance and require rigorous scientific investigation to provide a solution to significant public health problem that is disc degeneration.

Compliance with ethical standards

Conflict of interest None.

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