The role of inflammation in sciatica: the contradictory effect of macrophages

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Summary

It is highly likely that sciatica symptoms due to lumbar disc herniation are not only caused by mechanical compression of the nerve root, but also by pain inducing elements from inflammatory processes. This inflammatory response can be induced by macrophages that infiltrate the disc as a consequence of the herniation. By contrast, macrophages are also thought to influence recovery through resorption of the disc material. Hence, the presence and behavior of macrophages can have a strong influence on pain and recovery. Macrophage behavior depends on their differentiation, which can be polarized into either M1 or M2 macrophages: the M1 type being associated with pro-inflammatory processes and M2 with anti-inflammatory processes. In a systematic review, we demonstrated that high levels of M1 related pro-inflammatory cytokines (TNF-α, TNFR1, IL-6, IL-8, IFN- γ) were all associated with higher pain scores. In contrast, we showed that high levels of M2 related cytokines IL-4 and IL-10 associated with lower VAS scores. No associations were established for TGF-β. Moreover, presence of macrophages in general (CD68+) was associated with lower pain scores during follow-up.

Now that it is clear that macrophage infiltration in the disc matters for clinical recovery, we further verified their importance in recovery with radiological evidence. In a retrospective histological study, we assessed how macrophage infiltration affected the rate of resorption on MRI between baseline and one year post surgery and found that the degree of macrophage infiltration was not associated with herniation size at baseline, but significantly associated with reduction in size of the herniated disc at one-year post surgery.

Next, we proceeded with finding markers that predict the extent of macrophage infiltration and their behavior. The first marker of interest was the type of the herniation, complete extrusion versus disc bulging. The former was expected to result in more macrophage infiltration due to a higher exposure to the systemic circulation. The second was the presence of Modic changes (MC), which symbolizes fibrotic and/or inflammatory changes in the endplate. MC are believed to correlate with a pro-inflammatory environment, therefore a higher percentage of M1 macrophages is to be expected and thus inferior clinical outcomes. Firstly, we found that the degree of macrophage infiltration was higher in extrusion in comparison to bulging (protrusion) discs. Secondly, with regard to the clinical outcomes: we found the presence of MC to be predictable for macrophage behavior: For those without MC, macrophage infiltration (CD68) resulted in reduced leg pain during follow-up after surgery, but in patients with MC2 the opposite was seen. In this group, patients with considerable inflammation were significantly more disabled compared to patients with mild inflammation. When data was subsequently split for extruded and bulging discs, similar effects on clinical outcome were seen for extruded discs, but no significant effects in bulging discs. Taken together, this shows that macrophage infiltration most often occurs in extruded discs, and that, for many patients, macrophage infiltration means a quicker resorption of the disc and a quicker relief of pain symptoms. However, for patients with MC, detrimental macrophage behavior was observed, which resulted in poorer recovery after surgery.

In search of a more sensitive marker for inflammation than disc extrusion, we evaluated the reliability of gadolinium enhancement on MRI as a marker for macrophage infiltration. Degree of inflammation by macrophages was not associated with gadolinium enhancement of nerve roots or herniated discs. Therefore, gadolinium enhancement was regarded as an unreliable indicator for inflammation of disc herniation or nerve root in patients with sciatica.

Because MC are associated with a detrimental effect of macrophage infiltration on clinical outcomes, we proceeded by exploring the pathophysiology of herniated discs with MC in the adjacent endplate. Moreover, since MC involves the endplate, we also evaluated the effect of endplate avulsion, which is a mechanism of herniation in which the integrity of the disc is lost due to a tear in the endplate instead of a tear in the annulus fibrosus. In our proteomic and bioinformatic study, we were able to identify that MC were associated with an altered protein expression that signified a decrease in the pathway 'detoxification of reactive oxygen species (ROS)' (a decrease in the elimination of toxic products) and a decrease in the complement system and immune system. In contrast, compared to an annular tear, avulsion of the endplate was associated with an increase in coagulation and 'detoxification of ROS'. Together, this signifies that endplate avulsion is a traumatic injury of the endplate which is followed by a wound healing response. In contrast, MC illustrates a decrease in a healthy immune response, either through a decrease in quantity or an altered functionality/differentiation of factors involved in the immune response. When this result is combined with our previous findings that MC predicted a detrimental effect on the clinical outcome if macrophages had infiltrated, an altered differentiation seems to be the most likely cause for the 'decrease in a healthy immune response'.

This altered differentiation profile was further assessed in a histological pilot study. This study showed, in line with the previous findings that the main type of macrophage infiltration was M2 (CD163+), and that the percentage of M2 was lower in patients with MC as compared to those without.

In this study, we demonstrated that macrophages play a crucial role in lumbar disc herniations; in most cases, macrophages differentiate towards M2 and thereby speed up resorption of the disc to relieve patients from their sciatic symptoms. However, patients with MC are less likely to differentiate towards M2, which results in increased disability and reduces the rate of recovery. The pathophysiology behind the detrimental effects of MC is still not completely understood. Recent studies have found that MC are associated with a bacterial infection of the disc, which is known to shift macrophage differentiation away from M2 and towards M1, and thus may function as an explanation for the altered differentiation pattern in MC patients. Everything considered, we provide 3 subgroups of disc herniation patients that may benefit from different treatment approaches: firstly, the patients without macrophage infiltration, who have a herniated disc that will likely resorb slowly and may benefit from early surgery; secondly, patients with a M2-dominant inflammation response, who most likely have a herniated disc that will resorb spontaneously and will benefit from prolonged conservative care; thirdly, patients with a detrimental M1-dominant inflammation response, who's herniated discs are unlikely to resorb quickly, but decompression surgery will also not completely satisfy these patients as there is still an inflammatory response that may irritate the nerve root. This third type is likely to require additional antibiotic treatment, in case of a bacterial infection, or, if the inflammation in the disc has an autologous nature, may require arthrodesis surgery. In order to implement such personalized treatment strategies, we first need to discover non-invasive biomarkers, using MRI or blood samples, that can recognize macrophage infiltration and differentiation with high sensitivity and specificity. Moreover, role of bacteria and other causes that may influence macrophage differentiation in the disc should be further explored. Hence, in the last chapter, we outlined a new study protocol that aims at finding these biomarkers and unravelling the causes for alterations in macrophage differentiation: Effect of Infection, Modic and Inflammation on Clinical Outcomes in Radiculopathy (EIMICOR). Hopefully, with the results of this new trial, we will be able to implement personalized treatment strategies that will significantly improve recovery rate and reduce disease burden in all sciatica patients.