Introduction: Pathology from intervertebral discs is thought to result in pain and radiculopathy. Surgical intervention based upon imaging findings and symptoms has become increasingly common. Despite the best intentions by the surgeon, failed spinal syndrome is an increasing problem as a result of treatment. The extent to which its diagnosis and consequential surgical treatment is appropriately provided is presently limited by the false-positive rates and current precinics of radiological and clinical correlations. The recent failure of human clinical trials to demonstrate efficacy of anti-TNFalpha treatment for herniated nucleus pulposus (HNP)-induced sciatica highlights not only our continued ignorance of the mechanisms underlying this pathology, but also the danger of direct extrapolation from rodent studies to human pharmacotherapy. These factors and the lack of consensus as to the best treatment strategy clearly accentuate our need for biomarkers. We investigated the profile of inflammatory cytokines in patients with HNP-induced sciatica as compared to those with low back pain (LBP) alone.

Materials and Methods: 46 patients referred for back or leg pain were evaluated by physical exam and MRI. Patients were then divided into 2 groups based on the following criteria: Group 1: Radiculopathy as the primary complaint and negative Waddells signs and neurocompression on MRI correlating to the symptoms and signs. Group 2: LBP as the primary complaint or radiculopathy with > 3/5 positive Waddells signs or no neurocompression or neurocompression that did not correlate with symptoms and signs.

The epidural space was lavaged under fluoroscopy utilizing a technique previously described(1). Three ml of saline was infused into the epidural space and withdrawn. This lavage (1-2 ml) was placed in sample tubes and frozen until analysis. The patient was then administered an injection of a corticosteroid. Patients were followed for 3-6 months. Pain relief was graded as "excellent," "good," "fair," and "poor." The concentrations of 18 inflammatory cytokines from these samples were quantified using a Bioplex immunoassay.

All patients were assessed by physical exam, MRI, reported symptoms, VAS, signs of nonorganic back pain, SF-36 and Oswestry LBP index questionnaires. The concentrations of 18 cytokines were measured in lavage samples of all patients and asymptomatic volunteers.

The concentrations of 18 cytokines were measured in epidural lavage samples of all patients and asymptomatic volunteers utilizing a bioplex assay.

The response to an epidural steroid given at the time of lavage was monitored based therapeutic development that may allow long-term pain reduction thereby circumventing invasive surgical treatment.

Results: 23 patients satisfied criteria for Group 1; and had MRI findings consistent with neurocompression (HNP and/or stenosis). This group consisted of 14 males and 9 females with a mean age (± SD) of 46.2 ± 13.2 years (range 25-78), reporting mean visual analog pain scores (VAS, ± SD) of 6.6 ± 1.7. Thirteen patients reported left-sided symptoms while 10 reported them on the right, averaging 10.3 ± 9.1 weeks duration prior to the epidural lavage procedure. Seventeen patients reported radiculopathy only, while 6 patients also reported associated LBP. All patients had a positive straight leg sign and no patients were found to have somatization (defined as ≥ 3/5 Waddell’s signs). Five patients in this group were being treated under worker's compensation for an on-the-job injury. Mean (± SD) SF-36 and Oswestry scores were 54 ± 16 and 39 ± 19, respectively.

24 patients satisfied criteria for Group 2 and had a myriad of MRI abnormalities which included the following: Nine patients with HNP only (without neurocompression), 4 with stenosis, 6 with disc degeneration, 1 with spondylolisthesis, 1 with spondylosis, and 3 with mild disc bulges without neurocompression. This group consisted of 13 males and 11 females with a mean age (± SD) of 44.3 ± 13.5 years (range 19-70), reporting mean visual analog pain scores (VAS, ± SD) of 7.7 ± 1.4. Ten patients reported left-sided symptoms, 10 reported them on the right, and 4 reported bilateral pain, averaging 15 ± 11.2 weeks duration prior to the epidural lavage procedure. Seven patients reported radiculopathy only, 4 patients reported LBP only, 12 patients reported both LBP and radiculopathy and one patient reported pain in many body regions in addition to the low back and legs. Seven patients had a positive straight leg sign on the same side as the reported symptoms, 1 had a positive sign on the contralateral side. Twelve patients in this group were found to have ≥ 3/5 positive Waddell’s signs. Nineteen patients in this group were being treated by worker's compensation insurance for on-the-job injury and 1 patient was injured in a car accident with litigation pending. Mean (± SD) SF-36 and Oswestry scores for this group were 45 ± 20 and 54 ± 22, respectively.

3 asymptomatic volunteers also underwent epidural lavage for cytokine study.

An inflammatory cytokine was present in all epidural lavage samples of patients from Group 1. The measured concentrations of the identified biomarker was 1470 ± 547 pg/ml (mean ± SEM) (median = 175 pg/ml; range = 0 – 7363 pg/ml) This cytokine was found in very low concentrations or undetectable in samples from Group 2 and negative controls. The mean concentration was significantly greater (P < 0.01, ANOVA) in samples from Group 1 as compared to Group 2. Furthermore, all of the subjects in Group 1 reported either an "Excellent" or "Good" response to the epidural steroid injection, as compared to subjects in Group 2, where none reported "Excellent," 2 reported "Good", 5 reported "Fair" and 16 reported "Poor".

Discussion: We have identified a biomarker and potential therapeutic target in the epidural space of patients with radiculopathic pain and MRI-confirmed neurocompression thought to result from HNP. This biomarker was successful in predicting the degree to which each patient responded to epidural steroid injection. These findings may enable future improvements in the selection of patients for surgical and/or steroidial management. In addition, the findings may enable evidence-based therapeutic development that may allow long-term pain reduction thereby circumventing invasive surgical treatment.


<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Group 1 (Radiculopathy)</th>
<th>Group 2 (Back Pain)</th>
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<tbody>
<tr>
<td>IL-6</td>
<td>Mean: 10, SD: 3.6</td>
<td>Mean: 10, SD: 3.6</td>
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<tr>
<td></td>
<td>SEM: 1.4</td>
<td>SEM: 0.8</td>
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