Title
Neuropathic pain in multiple sclerosis

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Neuropathic pain in multiple sclerosis

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Abstract:

Multiple sclerosis (MS) is a chronic neurologic disease characterized by autoimmune destruction of myelin, a sheath-like material that insulates and protects nerve fibers. A significant portion of patients with MS experience severe chronic pain that is neuropathic in nature. Preclinical studies have recently demonstrated that a specific degradation product of myelin basic protein (MBP), one of the major targets of the autoimmune response in MS, is capable of producing neuropathic pain. In particular, MBP cryptic antigenic epitope, which is hidden in intact MBP, is exposed and released post-nerve injury by the activity of matrix metalloproteinase 9 (MMP-9) and produces neuropathic pain. The purpose of our study is to determine if levels of the degradation product of MBP and antibodies against it correlate with the presence and severity of chronic neuropathic pain in patients with MS as well as to find out if levels of matrix metalloproteinase 9 in urine can be used as a marker of pain in MS patients.

Introduction:

Multiple sclerosis is a demyelinating autoimmune disorder that affects the central nervous system. The disease usually presents itself in young adulthood. There are four types of MS: relapsing-remitting, primary-progressive, secondary-progressive, and progressive-relapsing. Typically, MS patients experience several episodes (relapses) over time that can improve on their own. However, approximately 5 to 10 percent of adult MS patients have the primary-progressive form of MS, which presents with gradual accumulation of disability from the onset, without superimposed acute relapses (Holland et al, 2011). The most common
symptoms of the disease include optic neuritis, numbness, paresthesia, weakness, and internuclear ophthalmoplegia.

Studies have found that greater than 50% of MS patients suffer from chronic pain (Waldemar Brola et al, 2014). Patients suffering from advanced states of multiple sclerosis are the most likely to also suffer from pain that impairs their daily function. The type of pain patients experience varies. The most common types include back pain, tonic spasms and Lhermitte’s sign (intense burst of electric shock-like pain that runs down the back into the arms and legs). Other types of pain associated with MS are central neuropathic pain and unilateral or bilateral craniocervical pain due to lesions of the central connections of the trigeminal nerve or upper cervical nerve roots. In all these cases the pain may be continuous or paroxysmal. Other associated sensory disturbances may include dysesthesia, hypoesthesia, anesthesia, hypoalgesia, and paresthesia. Older age and female gender as well as progressive disease are some of the risk factors for pain in MS (Waldemar Brola et al, 2014).

Pain in MS falls into one of two categories, nociceptive or neuropathic. Neuropathic pain is more likely to be chronic and debilitating. Previous research suggests that the neuropathic pain associated with MS may be due to autoimmune attacks on myelin, the insulating material surrounding neurons in both the central and peripheral nervous systems (Lui et al., 2012). More specifically, the neuropathic pain may be produced when myelin basic protein, an essential and major component of the myelin sheath, is degraded. The resulting nerve damage in the brain and spinal cord leads to hyper-excitability of the pain pathways.
Researchers have categorized the neuropathic pain that results from the demyelinating lesions in the central nervous system as central neuropathic pain. It is thought that the neuropathic pain is related to T cell lymphocyte infiltration of the spinal cord and brain as well as peripheral nerves (Lui et al., 2012). Previous studies revealed that Th1-mediated cells, in particular, lead to peripheral neuropathies in humans by way of autoimmune attacks on peripheral nerves (Lui et al., 2012). Researchers also found that Th1-mediated cells lead to pain in animal models that have been immunized by myelin basic protein and/or myelin peptides (Lui et al., 2012). It is now believed that the autoimmune response to the breakdown of MBP results in the clearance of these peptides and regeneration of the peripheral nerves.

Shubayev and Strongin have evidence that a specific fragment of MBP contains a cryptic antigenic epitope that is hidden in intact MBP but is exposed and released after nerve injury by the activity of matrix metalloproteinase 9 (Shubayev et al, 2009). They have further evidence that this cryptic MBP epitope is capable of producing neuropathic pain in naïve animals (Chernov et al., 2015; Nishihara et al., 2015; Lui et al., 2012; Kim et al., 2012). Nimmerjahn showed that the cryptic MBP epitope peptide initially forms a complex with anti-epitope antibodies and the peptide-antibody complex can bind to the Fc receptor(s), most probably to Fc-gamma receptor type I (FcγRI/CD64) in Schwann/neuronal cells, resulting in the onset of pain (Nimmerjahn and Ravetch, 2011; Nimmerjahn and Ravetch 2008; Nimmerjahn and Ravetch, 2006; Qu et al., 2011). The molecular and cellular processes that occur in peripheral nerve injury models in animals may be the same ones that bring upon pain in MS patients.
We believe that released cryptic MBP epitopes result in enhanced systemic levels of both the specific antibodies and epitope-antibody complexes, resulting in agonizing pain from which MS patients frequently suffer. The aim of our study is to test our hypothesis by quantifying levels of MBP proteolytic fragments, their respective antibodies, and MMP-9 activity in serum and urine samples collected from patients with MS and severe chronic neuropathic pain compared to patients with MS who do not have chronic pain. We hope that these studies can help us correlate levels of specific MBP fragments and their respective antibodies with the severity of neuropathic pain in patients with MS. Another aim of our project is to determine if increased MMP-9 levels in the patients’ urine can be used as an early predictive marker of the pain onset.

**Research Design and Methods**

The aim is to recruit up to a total of 45 female subjects for the study: 20 patients with MS and severe chronic neuropathic pain, 20 patients with MS without severe chronic pain, and 5 healthy volunteers.

All subjects underwent a detailed medical history and physical examination. The medical history included review of the natural history, severity, and treatment of multiple sclerosis, as well as completion of the Neuropathic Pain Symptom Inventory (NPSI), a questionnaire designed to assess multiple dimensions of a patient’s pain experience (Bouhassira et al., 2004). Physical examination included quantitative sensory testing of painful areas; control subjects underwent testing of the foot on the dominant side. Subjects’ written consent for participation was obtained and the study was approved by the Institutional Review Board at the University of California, San Diego.
The following sensory tests were performed:

1. Tactile allodynia – a Von Frey fiber of 5.18g attached to pen-like instrument is applied to skin until the fiber bends. Test is repeated twice for a total of three times. Pain intensity is determined by the patient and quantified in terms of Visual Analogue Scale from 0 (no pain) to 100 (worst imaginable pain).

2. Dynamic allodynia – application of a 1 inch foam brush to skin. Pain intensity is determined by patient and quantified in terms of Visual Analogue Scale.

3. Thermal hyperalgesia – determined by reported pain intensity, quantified in terms of Visual Analogue Scale, to application of a 42 degree C stimulus generated by the thermal probe that is part of the TSA-II NeuroSensory Analyzer.

4. Heat pain threshold – determined using the thermal probe and TSA-II NeuroSensory Analyzer. The probe is maintained at 32 degrees C, applied to the test site, and temperature of the probe increased at a rate of 1.5 degrees C per second up to a maximum cut-off of 50 degrees C, sufficient to elicit pain in most subjects without damaging tissue. When the subject experiences pain, they press a switch that records the heat pain threshold and reverses the temperature change, returning to a neutral temperature of 32 degrees C.

5. Pressure pain threshold – determined using a Wagner FPK manual pressure algometer. This is a hand held device with a 1 cm rubber tipped plunger mounted to a calibrated spring that determines the minimum force (in grams) required to produce detectable pain. The test is performed three times.
At the conclusion of the examination, subjects underwent venipuncture to collect a sample of blood (5mL) and provide a sample of urine (10mL) for quantification of MBP fragments, their respective antibodies, and MMP-9 activity. Fluid samples are analyzed by Drs. Shubayev and Strongin at laboratories at the Sanford-Burnham Medical Research Institute. Aliquots of plasma are obtained and antibodies specific for the cryptic nociceptive MBP fragments are captured. The MMP-9 activity is measured in the urine samples.

Once all 45 patients are seen, the clinical data obtained will be averaged for each subject group (MS pain, MS no pain, control) and used for descriptive purposes in our lab. Our partners, Drs. Shubayev and Strongin, will quantify the intensity of antibody binding and express it as a percentage of activity in control samples (healthy volunteers). Antibody and MMP-9 activity will be analyzed for significant group differences using one-way analysis of variance with Tukey’s post-hoc testing. P<0.05 will be used to determine significance.

**Results:**

Sensation Assessment

Multiple Sclerosis with pain

<table>
<thead>
<tr>
<th>Exam</th>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foam Brush</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Von Frey 5.18</td>
<td>2</td>
<td>6</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>Heat Pain Intensity</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QST Pain Threshold</td>
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<td>50</td>
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<tr>
<td>Algometer</td>
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<td>14</td>
<td>16</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Control
As we have only seen two patients thus far, we are not able to make any conclusions on the results. At first sight, the current pain scores do not show a significant difference between the control and the MS with pain patients. In fact, the one MS with pain patient has higher QST Pain threshold average than our control and is able to tolerate higher algometer pressures. Foam brush and heat pain intensity have provided no useful values in the two patients we have seen thus far. The results of MMP-9 and MBP are not available for correlation with pain scores and sensitivity tests at this time.

Discussion:

There has been great progress in elucidating the mechanism behind neuropathic pain in multiple sclerosis. In particular, it has been shown that MMP-9 and MBP play vital roles in the activation of neuropathic pain. However, the correlation between neuropathic pain intensity and MMP-9 and MBP levels have not yet been established. Given the growing evidence in support of the roles of MMP and MBP in activation of neuropathic pain we do expect there to be a correlation, however, at this point we do not have enough patients to

We believe our tests will help elucidate this unknown relationship. Our study may also reveal which type of pain, pressure vs heat vs mechanical, occurs most frequently in MS patients suffering from chronic neuropathic pain.

If our study does indeed find a correlation between MBP and/or MMP and pain intensity in MS patients, this could have a profound affect on future research and clinical implications. Simple blood and/or urine tests could potentially provide useful predictive markers of chronic neuropathic pain in MS patients.

References


