Title: Regional Pain Syndrome: Need for integrative modalities to aid long term pain control

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Objectives:

1. Discuss chronic pain prevalence and pathophysiology in children, with focus on CRPS
2. Discuss diagnostic criteria and evaluation of CRPS
3. Review use of opioids, adjunct medications, and invasive procedures including nerve blocks, epidurals and sympathetic blockade in the setting of CRPS
4. Utilize an interdisciplinary team approach, and include integrative medicine, such as hypnotherapy, as a treatment for chronic, acute, and acute exacerbations of chronic pain.

Case study:
A 16 year old 70kg otherwise healthy female presented to the emergency department with severe burning left upper extremity pain. She was screaming, crying and writhing in pain. Light touch of even clothing touching her arm caused her to scream louder. She had no history of injury to the extremity, but was an avid athlete and participated in horseback riding. No prior history of such pain, no other medical problems. On physical exam, the arm was discolored, with edema extending from the fingers to above the elbow.
Cases study (continued):
The patient reported extreme sensitivity to temperature changes, i.e. cold weather. No trophic changes of the skin, nails and hair patterns were noted. No signs of temperature asymmetry were noted. The ER physicians administered IV hydromorphone and IV lorazepam, with minimal change in pain levels. She eventually became sedated with larger doses of medication, but upon arousal, she would again begin complaining of significant pain in the left arm. Ketorolac was administered, also with minimal effect. Labs were drawn. Results follow.

Questions:
What should the ER do? What medical or surgical evaluations would you suggest? What other physical exam findings may be pertinent?
### Table 1: Laboratory Results

<table>
<thead>
<tr>
<th>Patient Result</th>
<th>Normal Range</th>
<th>Patient Result</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>&lt;0.3 mg/dL</td>
<td>AST</td>
<td>22 U/L</td>
</tr>
<tr>
<td>CK</td>
<td>0-215 U/L</td>
<td>Alk Phos</td>
<td>74 U/L</td>
</tr>
<tr>
<td>LDH</td>
<td>84-246 U/L</td>
<td>ALT</td>
<td>42 U/L</td>
</tr>
<tr>
<td>Aldolase</td>
<td>1.2-7.6 U/L</td>
<td>Blood cultures obtained</td>
<td></td>
</tr>
</tbody>
</table>

#### Questions:
What is your differential diagnosis at this point? What further studies would help you make a diagnosis?

#### Case Study (continued):
An MRI of the forearm and elbow was obtained; it was normal. She was taken to the operating room for muscle biopsy and an interscalene nerve block with bupivacaine was performed under general anesthesia with ultrasound guidance. The images follow below. Upon awakening in the PICU, the patient had a dense block with complete numbness and no complaints of pain in her arm.

#### Questions:
What is neuropathic pain? What are the mechanisms? What is CRPS? How does one make a diagnosis of CRPS? What is the pathophysiology of CRPS? What is the incidence of CRPS in pediatrics? How is CRPS different in pediatric that adults? What are the difficulties in diagnosis for CRPS? How long do patients typically have pain before diagnosis and treatment?

#### Case Study (continued):
The patient slept without problems overnight, but in the morning, again began complaining of pain, unresponsive to IV opioids. When she was not sleeping, the patient was screaming at her parents and the house staff.

#### Questions:
What are options for immediate treatment of pain?

#### Case Study (continued):
Due to an inability to control pain without sedation, the patient was placed on scheduled lorazepam. Tramadol was found to decrease her pain to moderately tolerable levels. A ketamine drip was continued for a 5 day course with significant resolution of pain. She was able to begin moving the arm, and was agreeable to continuing physical therapy as an outpatient. She was started on gabapentin with instructions to follow-up with an outpatient pain facility for further care.

#### Questions:
How would you treat her as an outpatient? What are the best pharmacotherapeutic strategies for pediatric CRPS? What is the safety/efficacy of invasive interventions – nerve blocks? Sympathetic blocks? Epidurals? Spinal cord stimulation?

Case Study (continued):
After 6 months, the patient reappeared at the emergency room, again screaming and writhing in pain. Mom reported that the patient had attempted outpatient follow-up at an adult pain clinic, where 5 sympathetic nerve blocks had been performed with minimal benefit. The patient had also been placed on amitriptyline, topical lidocaine patches, tramadol, and had tried a TENS patch. Mom reported that the patient had daily pain, and had not been using the arm much at all, but that at least she had been able to continue her school activities, until the prior 12 hours, when the pain became unremitting. On physical exam there was some diffuse edema in the limb, but no evidence of the discoloration noted on initial presentation. Motor function of the hand was also somewhat decreased.

The emergency department transferred the patient to the pediatric intensive care unit in order to provide medical sedation while improved pain control was attempted.

Questions:
What would you do now? How do you acute treat her pain? The patient continued to scream and disrupt all nearby inpatients despite IV opioids. Each time an IV anxiolytic wore off, she again continued to scream and was unable to interact with medical staff.

What aspects of this patient's care have been relatively overlooked? What would you do different in her outpatient management? What non-pharmacologic therapies would you advise? What are the adverse consequences of inappropriate or inadequate treatment of neuropathic chronic pain?

Case Study (continued):
The patient was kept medically sedated with dexmedetomidine and propofol. Another course of IV ketamine was initiated. Psychology was consulted and revealed many emotional triggers for her pain episodes. She underwent significant psychological interventions, including self-hypnosis training and cognitive behavioral therapy. With self-hypnosis she was able to decrease the severity of her pain exacerbations, and found greater control in her own pain management. She was discharged on oral dextromethorphan, gabapentin, and tramadol with stable pain and assigned to regular follow-up with psychology and physical therapy.

Questions:
How can integrative modalities be used to interrupt an episode of acute pain? Can you describe how you would treat pain using non-pharmacotherapeutic methods? What is hypnosis? How is it beneficial in as a pain management modality? What are other integrative treatment modalities that are beneficial in managing chronic pain?

Discussion:
Complex Regional Pain Syndrome (CRPS) has been a perplexing disease since the mid-1800's. Some of the clearest descriptions come from the American Civil War where the low-velocity, high-mass missiles...
used in the battles were quite effective in inducing neuropathic pain associated with significant autonomic dysregulation. Medical history has struggled to come to a consensus about the pathophysiology of the disease, and diagnostic considerations are still somewhat unclear. Clinically, the disease is characterized by pain out of proportion to the inciting event, and signs of autonomic instability either by history or on examination are required to make the diagnosis. As CRPS still remains a diagnosis of exclusion, many tests are performed prior to treatment initiation. Specialists in orthopedics, pediatrics, rheumatology, neurology and emergency are often consulted prior to referrals to pain clinic. It may take 3-9 months for a patient to be referred to the appropriate specialist for treatment of CRPS – at which point, significant pain is already pre-existing, often muscle wasting from inactivity is present, and numerous other psychological aspects of the pain need to be addressed. This later diagnosis is difficult as trophic changes tend to occur as the disease progresses, and symptom resolution occurs much more rapidly in those diagnosed early (<3months) than those diagnosed later (>6months).

Interventions in adult CRPS patients often include sympathetic blocks, spinal cord stimulators and implant pumps. There is a belief that nerve blocks should be done very early in the treatment. The evidence, however, for any of these interventions is very weak. CRPS in children and adolescents typically has a very good response to rehabilitative treatment (physical therapy, occupational therapy, and cognitive behavioral therapy). Blocks are stressed as best to place as indwelling catheters during inpatient rehab, in an attempt to provide a pain-free period so the patient may progress in physical or occupational therapy. The primary benefit of a block is to provide transient relief of pain, and allow the patient to participate in therapy. The adult literature states that spinal cord stimulation should be recommended only for patients with CRPS have failed more conservative evidence-based treatment; insufficient evidence is available in the pediatric population to obtain a high level recommendation, but it does have the advantage of being nondestructive and completely reversible.

Many medications have been tried, and often reported as helpful in the adult CRPS literature, but few have been subjected to the scrutiny of a double-blind, randomized controlled trial. There are no prospective randomized clinical trials of any medications in the treatment of CRPS in children. Typically, treatment with an anti-epileptic compound (i.e. gabapentin) or antidepressant (i.e. amitriptyline) is combined with an abortive medication in cases of acute exacerbations. Medications common for outpatient therapy include gabapentin, pre-gabalin, carbamazepine, and NSAIDS. The lidocaine patch may be useful in some localized CRPS phenomena, though typically an entire extremity is affected. Opioids provide little benefit, and prolonged therapy with such is associated with multiple problems.

Exacerbations of intense pain as seen in this case are unusual and, here, were managed with deep sedation. Ketamine was initially chosen as there have been scattered reports of some response in CRPS to a daily course of ketamine infusions using anesthetic and sub-anesthetic doses. The effect of ketamine on the NMDA receptor may be of some import. Dextromethorphan is also an NMDA receptor agonist, and has been used in high doses as a part of outpatient therapy, with little evidence for or against. Acute exacerbations are also occasionally treated with lidocaine infusion, with continued oral mexilittle therapy.
Hypnosis is one modality that can be of use in chronic pain. The patient often experiences a loss of control during the progression and treatment of their pain. These psychological aspects need to be addressed. Teaching self-hypnotic skills can help the patient regain some measure of control over their own pain process, and provide skills which the child can continue to use to help themselves. Hypnotic suggestion can be used to target specific aspects of chronic pain, such as catastrophizing, and can be a valuable adjunct to other therapies.

Ultimately, pharmacotherapy is less efficacious in chronic pain syndromes, and effective treatment requires a multidisciplinary approach using physical and occupational therapy, nutrition, good sleep hygiene, and psychological approaches such as cognitive behavioral therapy.
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