A Complex Case of Chronic Pain

Date Created: May 7, 2020
Authors: Zimmerman, BJ, McGregor, AJ

Case Overview

A 43 y.o. female patient presents with persistent left arm pain which has been worsening. She was discharged from a behavioral health hospital 7 days ago and since then has been living with her daughter. Her daughter reports that the patient is always complaining of LUE pain, but in the last few days it has been more severe and she has had trouble using it. Five days ago she was seen for a medication refill. She had LUE pain then as well, with an exam that was documented as normal except for tenderness; she declined XR shoulder saying “they do them all the time”. Today her friend brought the patient in because she was distraught, “speaking gibberish”, and complaining of an exacerbation of her baseline left shoulder, neck, and chest wall pain. She says the confusion started along with the left sided pain. She says her LUE is always weak, tender, and swollen.

Pertinent Medical History

- IDDM
- HTN
- Anxiety
- Depression
- PTSD
- Chronic L “shoulder” pain after shoulder surgery four years ago (unknown procedure type)
- Not currently menstruating
- LMP unknown.

Medications

- Escitalopram
- Hydroxyzine
- Lisinopril
- Trazodone
- Lamotrigine
- Omeprazole

Relevant Vital Signs

Initially tachycardic (~100) and hypertensive (187/91). After hydromorphone, HR (~85) and BP (155/72) decreased.

Laboratory Evaluation

Drug screen negative, WBC, platelets and inflammatory markers (CRP and ESR) within normal limits.

Physical Exam

- Agitated, writhing, minimally speaking with staff. After pain meds: calm, following commands, coherent.
- Left neck TTP, L shoulder TTP, L clavicle TTP.
- LUE weakness, otherwise full strength. Otherwise normal neuro exam

Assessment

This is a 43yo non-menstruating female with several CVA risk factors (HTN, DM) and hx of chronic LUE pain who presents tachycardic, hypertensive, and distracted due to pain. Her primary concern is her chronic LUE pain which has been worsening, and her friend's concern was the pt's mental status. We note weakness, limited ROM, and allodynia in that limb on exam.

Differential Diagnosis: Stroke, septic arthritis, CRPS, neuropathy, trauma to LUE, arthritis, herpes zoster, malingering.

Testing

- CT/CTA normal.
- Shoulder XR unremarkable except for stable Hill-Sachs lesion and decreased mineralization.
- Previous CT from two years ago noted inflammatory stranding to right shoulder ("possibly related to dislocation").

Discussion

Pain is one of the most common complaints in patients presenting to the emergency department, and in light of the opioid epidemic, increased attention is being paid to individualized pain treatments based on the underlying causes of pain. One of the most fundamental individualizing factors easily garnered about a patient is their sex and gender. Men and women have different physiology, psychology, and socialization affecting the manifestation of pain. One such difference relevant to this case involves the role of sex hormones in modulating pain, specifically the protective effect of estrogen on pain, which occurs through upregulating opioid receptors and the release of endogenous opioids.[1] This could help explain why many conditions manifesting predominantly as chronic pain become more prevalent after menopause, less prevalent with pregnancy, and why differences in pain sensitivity between genders become more pronounced after age twelve.[2]

Complex regional pain syndrome (CRPS) is at least three times as common in women, and most of those patients are post-menopausal.[3] Researchers believe the reason females experience higher levels of chronic pain disorders and greater pain sensitivity in general is rooted in the interplay between the immune system and certain sex hormones including androgens and estrogen.[1,2] Immune system activation appears to have a central role in the pathophysiology of CRPS[4]; the current understanding is that there is an inflammatory response after physical trauma which leads to a cascade of nervous system changes.[4] Certain

inflammatory markers are significantly increased in both the acute and chronic phases of the disorder.[5] It has been suggested that early identification and treatment with anti-inflammatories may be able to prevent this disorder.[4]

The exact role of sex hormones in CRPS is not clear and has not been heavily studied. Besides the correlational demographic evidence presented above, one study of fifty-three CRPS patients and matched controls found higher CRPS rates in the 6-month postpartum period than in controls. They did not find a correlation with cumulative endogenous estrogen exposure, although it may have been underpowered to elucidate this relationship.[3] Hormone replacement therapy (HRT) has not been suggested as a therapy at this time.

The diagnostic criteria for CRPS (sn 0.85, sp 0.69) mandate pain disproportionate to the inciting event, no other better explanatory diagnosis, three of four symptoms, and two of four signs from the following categories: sensory, vasomotor, sudomotor/edema, motor/trophic. This patient meets criteria (symptoms, ¾ categories: allodynia, edema, weakness/decreased ROM; signs, 2/4 categories: allodynia, decreased strength/ROM). The patient has several risk factors for CRPS (female, post-menopausal, UE injury and surgery, PTSD, autoimmune disease), and a convincing story (extreme pain immediately following surgery and persisting, progressing to motor and sensory symptoms with subjective swelling, and in a gradually expanding but consistent distribution).

In addition to an increased likelihood of initially developing CRPS, females are more likely to have symptoms persist beyond one year from the inciting incident.[6] Malingering was considered given her dramatic improvement with opiates, however her vitals were consistent with pain, her tachycardia and mental status improved with opiates, she had no history of drug seeking behavior or drug abuse, had a negative drug screen, and had multiple years of documented complaints about pain/symptoms in the same distribution. The weakness was present at baseline for her but had not been previously documented, which in the setting of altered mentation/attention (which she attributes to pain), led to the stroke workup in triage. When her pain was adequately treated she was able to maintain a conversation. This patient routinely received imaging of her LUE and often got opiate pain medicine, but, at least as documented in the chart, CRPS had never been considered as an underlying cause by treating clinicians including the consulting neurologists on this encounter.

A diagnosis of CRPS is a clinical one and other testing is not necessary, however, it is interesting that experimentally certain types of imaging, biopsies, blood samples, and other bio-markers have been shown to correlate with CRPS.[4,5,7] Therefore, in this patient who has normal inflammatory markers, a diagnosis of CRPS must still be considered. CRPS Treatment involves patient education, PT/OT, psychosocial assessment, and pain management with low risk agents. Treatment failure and expanded options include various other modalities including interventional approaches. This patient had received none of these standard or adjunct treatments in the context of CRPS. She was undiagnosed, receiving significant radiation on a regular basis, and incurring significant healthcare expenditure. In cases of delayed diagnosis, treatment is less effective.

An area for improvement in this case would have been a more thorough menstrual history. This patient is 43, and would therefore have premature menopause if that was the cause of her amenorrhea. An accurate LMP should be established, and an exploration of possible explanations for her amenorrhea should be conducted as this relates directly to her chief complaint. It could be contributing to or affected by her chronic undertreated pain.

Men and women respond to pain and pain treatments differently.[8] Several studies have demonstrated that women have a relatively less significant response to μ-opioids such as morphine (or the hydromorphone our patient received) in certain settings.[8,9,10] Consistent with this physiology, when studied retrospectively in an outpatient population, women generally are written higher-dose prescriptions, and more often.[8,11] However, in the ED, women's pain is treated less aggressively and less promptly[12], and the author suspects that this phenomenon is exaggerated in those patients who are returning for the same symptoms regularly, as in this case. This is despite higher rates of chronic pain conditions and more sensitivity to acute pain among women. Finally, pain medication choice should be considered carefully in light of research demonstrating female's response to kappa opioid agonists/antagonists (e.g. nalbuphine, pentazocine, and butorphanol). Miller et al[13] found that females had a greater response to butorphanol than morphine at sixty minutes. Given our patients concomitant depression, and the general correlation between pain and depression, it should be noted that research is underway on the emerging role of kappa antagonists in treating depression.[14,15]

CRPS is one of many chronic pain disorders which can be differentiated from each other largely by a careful history and physical examination. Every effort should be made to explore possible diagnoses and explanations of any patient's pain, bearing in mind the sexually dimorphic physiology of pain and the changes in chronic pain conditions that correlate with fluctuating hormone levels. Clinicians should be familiar with the diagnostic criteria for CRPS, aware of the physiology and epidemiology of this and other similar chronic pain disorders, and be on the lookout for this uncommon disorder.

Follow Up

This patient was discharged before a diagnosis of CRPS was fully considered, so no specific recommendations were given for this condition, but general recommendations were given to follow up regarding further management of her chronic pain.

References

1. Pieretti S, Di Giannuario A, Di Giovannandrea R, et al. Gender differences in pain and its relief. Ann Ist Super Sanita. 2016;52(2):184-189. doi:10.4415/ANN_16_02_09
2. Sorge RE, Totsch SK. Sex Differences in Pain. J Neurosci Res. 2017;95(6):1271-1281. doi:10.1002/jnr.23841
3. de Mos M, Huygen FJPM, Stricker BHC, Dieleman JP, Sturkenboom MCJM. Estrogens and the risk of complex regional pain syndrome (CRPS). Pharmacoepidemiol Drug Saf. 2009;18(1):44-52. doi:10.1002/pds.1683

4. Birklein F, Ajit SK, Goebel A, Perez RSGM, Sommer C. Complex regional pain syndrome — phenotypic characteristics and potential biomarkers. Nat Rev Neurol. 2018;14(5):272-284. doi:10.1038/nrneurol.2018.20
5. Parkitny L, McAuley JH, Di Pietro F, et al. Inflammation in complex regional pain syndrome: A systematic review and metaanalysis. Neurology. 2013;80(1):106-117. doi:10.1212/WNL.0b013e31827b1aa1
6. Bean DJ, Johnson MH, Heiss-Dunlop W, Lee AC, Kydd RR. Do psychological factors influence recovery from complex regional pain syndrome type 1? A prospective study. Pain. 2015;156(11):2310-2318. doi:10.1097/j.pain.0000000000000282
7. Bharwani KD, Dik WA, Dirckx M, Huygen FJPM. Highlighting the Role of Biomarkers of Inflammation in the Diagnosis and Management of Complex Regional Pain Syndrome. Mol Diagn Ther. 2019;23(5):615-626. doi:10.1007/s40291-019-00417-x
8. Fullerton EF, Doyle HH, Murphy AZ. Impact of sex on pain and opioid analgesia: a review. Curr Opin Behav Sci. 2018;23:183-190. doi:10.1016/j.cobeha.2018.08.001
9. Loyd DR, Murphy AZ. The neuroanatomy of sexual dimorphism in opioid analgesia. Exp Neurol. 2014;259:57-63. doi:10.1016/j.expneurol.2014.04.004
10. Helal MA, Habib ES, Chittiboyina AG. Selective kappa opioid antagonists for treatment of addiction, are we there yet? Eur J Med Chem. 2017;141:632-647. doi:10.1016/j.ejmech.2017.10.012
11. Campbell CI, Weisner C, LeResche L, et al. Age and gender trends in long-term opioid analgesic use for noncancer pain. Am J Public Health. 2010;100(12):2541-2547. doi:10.2105/AJPH.2009.180646
12. Chen EH, Shofer FS, Dean AJ, et al. Gender Disparity in Analgesic Treatment of Emergency Department Patients with Acute Abdominal Pain. Acad Emerg Med. 2008;15(5):414-418. doi:10.1111/j.1553-2712.2008.00100.x
13. Miller PL, Ernst AA. Sex Differences in Analgesia: A Randomized Trial of μ versus κ Opioid Agonists. South Med J. 2004;97(1):35-41. doi:10.1097/01.SMJ.0000085743.68121.A9
14. Browne CA, Jacobson ML, Lucki I. Novel Targets to Treat Depression. Harv Rev Psychiatry. 2020;28(1):40-59. doi:10.1097/HRP.0000000000000242
15. Jacobson ML, Browne CA, Lucki I. Kappa Opioid Receptor Antagonists as Potential Therapeutics for Stress-Related Disorders. Annu Rev Pharmacol Toxicol. 2020;60(1):615-636. doi:10.1146/annurev-pharmtox-010919-023317