



Pain in Acute Hepatic Porphyrias

Pain is the number one reason people seek medical care. It is an invariable feature of attacks in the acute hepatic porphyrias (AHPs). The most common types of pain reported by patients during acute attacks are abdominal pain, but some patients report limb pain, back pain, and muscle pain. Pain is often excruciating during the attacks, and most patients report that their pain is severe, ranging between 8-10/10 in severity. While the exact mechanism of acute abdominal pain is still unknown, it is widely considered as a sign of impairment in the autonomic nerves within the gut wall which regulate the gastrointestinal motility. In between the attacks, pain remains to be the most common symptoms presenting in half to 2/3 of patients, with abdominal pain still being the most common. It is of utmost importance for patients and physicians to recognize the different types of pain as management differs between these types. Pain is also very common in some cutaneous porphyrias including the erythropoietic protoporphyria (EPP) and X-linked protoporphyria (XLP). Their cutaneous prodromal symptoms and excruciating painful episodes are both triggered by exposure to the sun and certain types of artificial light. The prodromal symptoms that occur on sun exposure include itching, tingling, stinging, and/or heat sensations on the area of exposed skin. These are the warning signals to immediately exit the sun as further sun exposure will lead to an excruciating and incapacitating pain that could last for 2-7 days.

Classification of pain:

In general, pain can be classified to:



- 1) **Nociceptive pain:** very common in AHP and cutaneous porphyrias like erythropoietic protoporphyria (EPP). It is often elicited by painful stimulation of normal tissue or tissues that are undergoing disease process. It can be divided into:
 - a) **Musculoskeletal pain:** mostly constant, worse with movement, dull aching, and localized.
 - b) **Visceral pain:** mostly deep aching, poorly localized, and intensifying in waves.
- 2) **Neuropathic pain:** common in AHP. It is caused by a disease in the nervous system. It is mostly burning, electricity like, stabbing, or shooting in quality. It is often associated with tingling, numbness, or other sensory phenomena like allodynia, perceiving pain when exposed to a normally non-painful stimulus, like a touch.
- 3) **Nociplastic pain:** which may occur in AHP and EPP after several years of suffering from the disease. This type of pain is caused by the gradual reorganization and remodeling of the pain sensitive structures starting from the pain receptors and up to the brain sensory centers. It is often spontaneous and does not need an eliciting factor to occur. It is mostly present all the time.

It is important to diagnose neuropathic pain early in the course of the disease, so appropriate and timely treatment is started. *Acetaminophen (Tylenol), aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS), and narcotics are NOT helpful for management of neuropathic pain.* It is worth noting that in neuropathic pain, the pain severity does not always correlate with the severity of actual nerve damage (also known as neuropathy). While Medical history and examination are key elements in the diagnosis,



some specialized tests can be ordered by your hepatologist, hematologist, neurologist, or pain management specialist **to objectively evaluate neuropathy in cases of porphyria and to help elucidate the origin of pain and whether it is neuropathic or not. Pain is mediated by the small nerve fibers under the skin and in the gut, which have no or just thin myelin insulation around them. These small nerve fibers cannot be assessed by the routine and readily available nerve conduction studies, which assess only the function of the large myelinated nerve fibers. Testing of the small nerve fibers can be achieved by:**

- 1) Skin punch biopsy: an easy and minimally invasive procedure that evaluates the structural abnormality of the small nerve fibers.
- 2) Sweat testing: quantitative sudomotor axonal reflex test (QSART) and thermoregulatory sweat test (TST) which are noninvasive procedures that assess sweat production as a physiologic function of the small nerve fibers.
- 1) Quantitative sensory testing (QST): This procedure tests the thresholds at which patients start to feel heat pain and cooling stimuli. However, it is not widely available in most medical centers and is dependent on the level of cooperation of the patient.

Treatment of pain in AHPs:

Treatment of pain in AHPs differs based on whether the patient is undergoing an attack or is in between attacks. In both cases, it is always imperative to check the safety profile of any pain medication in porphyria before using it. The Sweden Porphyria Center provides searchable databases that classify medications by their safety <http://www.drugs-porphyrria.org/index.php>.



A) During the attacks

Recognizing and understanding the extreme severity of acute abdominal pain is key in taking care of patients during acute attacks starting at the ER and during the entire hospital stay. Even in the setting of lack of objective findings in the medical examination or medical tests, the typically excruciating pain during the attacks should not be underestimated or overlooked. Opiates are often needed at scheduled intervals or via a patient-controlled analgesia [PCA] pump. The common acute side effects of narcotics, including slowed breathing/respiratory depression, confusion, and drowsiness should be monitored for while the patient is in the hospital.

Improvement in pain and ability to take oral pain medication are among the criteria for discharge from the hospital after acute attacks. Benzodiazepines like diazepam (Valium) can be combined with narcotics during the hospital stay to potentiate analgesia and relieve anxiety. Neuroleptics like chlorpromazine [Compazine] or promethazine [Phenergan] also help with the nausea and improve the patient's ability to start oral intake of food and nutrition and pain medications.

Treatment of acute attacks also includes adequate intake of energy/nutrition, including at least 300 g of carbohydrate, and IV heme, 3-4 mg/kg body weight/day, usually for 3- 5 days.

It should be noted that some AHP patients who have history of multiple previous attacks could sense the prodromal symptoms of an impending new attack and try to avoid going to the ER.

They could manage to do so by rest, trying to increase the carbohydrate content of their diet, and use prescribed narcotic pain medications to help with the pain, especially in the beginning. Some patients who are on prophylactic heme infusions may work with their physicians on getting one or two doses on demand of IV heme in an effort to avert an impending attack.

B) In between the attacks:



Prevention of further attacks is the mainstay of management of AHPs in between the attacks. Several lines of treatment are already available to achieve this goal, including healthy lifestyle, appropriate nutrition, hormonal therapy, prophylactic hemin infusions [Panhematin in the US and Heme Arginate (Normosang) in Europe and several other countries] usually given once every week or two, and the recently FDA approved monthly subcutaneous givosiran (Givlaari) injections. While opiates are the mainstay of treatment during acute attacks, safer alternatives should be employed as first line treatment options of chronic pain in between the attacks. The following options are safe in porphyria patients and are not known to provoke porphyric attacks:

- 1) Antidepressant medications like amitriptyline, mirtazapine, and duloxetine: they help with neuropathic and nociplastic pain. Mirtazapine has the advantage of improving appetite and duloxetine does not impair conscious level. It should be noted that these medications take 3-4 weeks to show benefit after initiating their oral intake.
- 2) Anticonvulsant medications like gabapentin and pregabalin: they both help with neuropathic and nociplastic pain. They can be taken on regular or as needed basis. They start acting immediately; however, they could cause some drowsiness initially. They both have a very wide range of dosage and titration up to the dose that produces the maximum clinical benefit with the least side effects is needed when prescribing these medications.
- 3) Muscle relaxants like baclofen which could also lead to drowsiness and titrating the dose to achieve the best clinical response with the least side effects is important.
- 4) Acetaminophen (Tylenol) and non-steroidal anti-inflammatory drugs can be used for mild to moderate nonspecific joint or low back pain. They are not helpful for neuropathic pain.
- 5) Non-pharmacologic pain management like biofeedback, acupuncture, and relaxation techniques, including yoga, were reported to be resorted to in chronic porphyria pain



patients in a study by Nail et al. in 2016. However, the benefit was temporary, and patients reported that these maneuvers never prevented an acute attack from happening.

Narcotics are best avoided in between the attacks; however, they continue often to be prescribed if other treatments do not provide much relief. Narcotics should be combined with non-pharmacologic and non-opioid pharmacologic therapy, and it is better for patients not to take them chronically, because of the development of physical dependence. In the current era of the opioid epidemic in the USA, most state medical boards have regulations that discourage physicians from prescribing chronic narcotic analgesics, and more importantly, combining narcotics with benzodiazepines for outpatient treatment because of the risk of respiratory depression and death. Treatment goals should be established with patients before starting and benefits/harms should be reevaluated with patients within 1 to 4 weeks after initiating outpatient narcotic treatment. Patients should have naloxone (Narcan) injection or nasal spray handy at home should opioid overdoses occur. Indeed, some patients could benefit from referral a pain management specialist to supervise the treatment plan and monitor for potential medication side effects.

In summary, determining if pain is neuropathic or nociceptive is important in management because medications like anticonvulsants and antidepressants can be helpful in neuropathic pain and can reduce the need for narcotics. Pain in acute hepatic porphyrias can be due to impairment of the small nerve fibers (neuropathic pain) while pain in cutaneous porphyrias is likely due to skin tissue injury (nociceptive). While severe excruciating pain is an invariable symptom of acute attacks of AHP, chronic pain occurs in some patients in between the attacks. Opiates play a major role in managing pain during the acute attacks but safer and more effective options like certain anticonvulsant and antidepressant medications should be tried first in between the attacks.



Multi-modal non-pharmacologic approaches are also worthy of consideration. The goal of management of chronic pain syndromes is to help patients develop coping mechanisms so that, despite chronic pain, they can continue to function and to perform their several roles with success. Patients who chronically use narcotic analgesics should always have naloxone available, and their families and friends should know how to administer it as required.

References and further readings:

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