Case Presentation: Neuropathic Pain

Initial presentation

A 68-year-old male with complaints of burning and tingling in both his feet that has been increasing in severity over the past 9 months.

History

The patient has a past medical history of diabetes mellitus type 2 for which he has been treated with diet, exercise, and Glucophage for the past 15 years. He admits that he does not always take his medication and he does not always check his blood glucose. He also admits that he indulges in sugary treats despite knowing it is not the best for him. He first noticed some mild tingly in his feet bilaterally about 3 years ago. Since that time he reports that the tingling has increased and is now painful. In addition, it now involves his lower extremities up to his shins.

He rates his pain a 7/10 on a numeric rating scale. He states it is becoming more difficult to wear his shoes because of the pain. In addition, he notes that the pain is worse at night. He denies any foot ulcers.

Physical examination

The patient is a slightly obese male who appears in moderate distress. His blood pressure is 145/85 and his heart rate is 85. His cardiac and respiratory examination is within normal limits. His abdomen is soft and non-tender, and he has normal active bowel sounds. Examination of the skin on his feet and lower extremities reveals slightly chapped skin of a ruddy complexion. He has decreased sensation to pin-prick on his feet bilaterally. He also has slightly decreased sensation to vibration bilaterally on his feet. His proprioception is within normal limits. His strength is normal in all extremities. He has decreased reflexes in his Achilles bilaterally. He has evidence of allodynia to light touch in a stocking distribution in his bilateral lower extremities. His HbA1C is 10.2.

What is this patient's likely diagnosis?

The patient has signs and symptoms consistent with diabetic peripheral neuropathy. Diabetic peripheral neuropathy is a symmetric distal sensorimotor neuropathy.

Neuropathy is one of the most common complications of DM. The prevalence of neuropathy increases with duration of the disease and with degree of glycemic control with poorer control being associated with higher risks. Diabetic neuropathy can all types of neurons including sensory, motor, or autonomic. When sensory neurons are affected, symptoms can include numbness, paresthesias, and pain. The symptoms tend to progress from the distal parts of limbs symmetrically. Common physical examination findings include loss or diminished

vibratory or proprioception in the toes or feet, decreased sensation to light touch and/or temperature in the lower extremities, loss of or decreased Achilles tendon reflexes.

What is the pathophysiology of pain secondary to diabetic peripheral neuropathy?

The main cause is a length-dependent axonopathy, primarily involving the distal portions of the longest myelinated and unmyelinated sensory axons. There tend to be relative sparing of the motor axons.[1-2] While the distal axonopathy is very common, proximal nerve dysfunction may also occur at the sensory ganglia.[3]

Which drugs can be used to treat this syndrome?

There is no cure for painful diabetic neuropathy (PDN), however methods can be used to help ameliorate symptoms. The first step in the treatment is establishing optimal glucose control. Neuropathic pain symptoms may improve with better glucose control but the improvement is often limited. The goal is therefore to prevent or to slow the progression of the disease.[4] Medications can also be used to help decrease pain. Medications used in the treatment of PDN include tricyclic antidepressants (TCA's), selective serotonin-norepinephrine reuptake inhibitors, calcium channel blockers—gabapentin and pregablin, opioids, and topical agents.

TCA's impact pain pathways by the following mechanisms: they prevent the reuptake of norepinephrine and serotonin; antagonize N-methyl-D-aspartate (NMDA), 5-HT, histamine, muscarinic, and alpha-adrenergic receptors; and inhibit sodium and l-type calcium channels.[5] TCA's are considered as first-line medications in the treatment of PDN.[6] TCA's have good evidence exhibiting analgesic efficacy in painful neuropathies compared to placebo.[7] The number need to treat (NNT) to achieve pain reduction of 50% in one patient for TCA's is between 2-3.[8] Amitriptyline at doses between 25-150mg per day has been shown to provide pain relief in PDN.[9] Sedation and anticholinergic effects are common side effects, especially in the elderly.

The selective serotonin-norepinephrine reuptake inhibitors (SNRI's) duloxetine and venlafaxine has also proven efficacious in the treatment of PDN. SNRI's mechanism of action is similar to that of TCA's, however they exhibit less side anticholinergic, antiadrenergic, and muscarinic side effects compared to TCA's. By effecting the balance of the serotonin and norepinephrine, they promote anti-nociception and decrease pro-nociception.[10] Duloxetine is FDA approved for the treatment of PDN. It is dosed at 30-60mg per day. Common side effects include gastrointestinal upset, headaches, and insomnia.

Gabapentin and pregablin also can be used to treat PDN. They both block the presynaptic calcium channel at the alpha-2-delta ligand, thereby inhibiting the release of excitatory neurotransmitters. They may also anatagonize NMDA receptors associated with pain signaling.[11] Pregablin is specifically approved by the FDA for the treatment of PDN. Pregablin is typically dosed at 50mg-75 mg once a day or twice a day to start and increased to 300mg per day in divided doses. The maximum dose is 600mg per day. The minimum effective dose for

gabapentin is 1600mg per day, but some patients may need a maximum of 3600 mg/day.[12] The starting dose is low typically 100-300mg per day and gradually increased until an effective dose is reached. Side effects include drowsiness, cognitive slowing, and peripheral edema. Both medications are renally excreted and thus dose adjustment is necessary in patients with renal compromise.

Opioids can also be used in the treatment of PDN, however they should be considered after other non-opioids medications have failed secondary to their abuse potential. Opioids bind to the mu and other opioid receptors on neuron cell membranes and thereby modulate descending and ascending excitatory pain pathways. Their primary targets are located in the spinal cord and central nervous system. Tapentadol is a partial mu agonist that also inhibits the uptake of norepinephrine.[13] It is approved by the FDA for treatment of PDN. If opioids are utilized specific predetermined goals for decreased pain and function should be established with the patient prior to the trial period. Regular screening for aberrant use through use of prescription monitoring programs and urine drug testing should also be undertaken.

Topical agents can also be used. They have the advantage of producing limiting side effects secondary to their limited systemic absorption. Lidocaine patches have been found to decrease pain and improve quality of life in patients with PDN.[14] Lidocaine blocks voltage-gated calcium channels which inhibits propagation of action potentials in neurons.[15] The patch is worn for 12 hours and then removed for 12 hours. A 4% formulation has recently been made available over the counter. Skin irritation is the most common side effect.

What non-pharmacologic treatments can be used?

Transcutaneous electrical nerve stimulation (TENS) has been shown to be effective in patients with PDN, however pain typically returns with cessation of the therapy.[16] Cognitive-behavioral therapy (CBT) and acupuncture have also shown some benefit.[17-18]

Neuromodulation can also be used. Dorsal column stimulation (also called spinal cord stimulation (SCS)) involves the implantation of small electrodes into the epidural space that are connected to a battery powered generator. If patients have improved function and pain relief during a trial-period, the system can be implanted internally. Its use has shown some benefit in the treatment of peripheral neuropathies. [19]

Follow-up

The patient was started on amitriptyline at a dose of 25mg per night and told to increase after 1 week to a dose of 50mg per night. He was also instructed to apply lidocaine cream to his painful areas. The patient returned and noted an improvement in his pain with minimal side effects from his regimen. He stated he was monitoring his blood glucose and taking his Glucophage as prescribed.

Summary

PDN can be difficult to treat, however a multimodal approach to treatment may help to alleviate symptoms. This approach includes improving glycemic control, oral or topical medications, behavioral therapies, and possibly neuromodulation.

Questions

1. Which of the following is a risk factor for developing painful diabetic neuropathy except?
    a. Poor glycemic control
    b. Short duration of disease
    c. Well controlled HbA1C
    d. Low carbohydrate diet

2. Common symptoms of PDN include all of the following except?
    a. Numbness
    b. Paresthesias
    c. Poorly localized pain distant from the source of injury
    d. Burning pain

3. The etiology of PDN includes?
    a. Length dependent axonopathy
    b. Spinal cord injury
    c. Extensive involvement of the motor neurons
    d. Proximal > distal axonopathy

4. Which of the following medications has has the least efficacy in the treatment of PDN?
    a. Gabapentin
    b. Amitriptyline
    c. Pregablin
    d. Paroxetine

Answers

1. A
2. C
3. A
4. D

References

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