Chronic Painful Diabetic Neuropathy in Emergency setting; A Case Report and Review of Literature

Akwue Tochukwu Anthony[a] MD, Aneke Chukwuebuka Somto[b] MD, Nwutobo Chidimma Rhoda[c] MD

[a]. Emergency Physician, Department of Emergency Medicine, Abha clinic and Emergency Hospital, Directorate of Health Affairs in Aseer region, kingdom of Saudi Arabia.

[b]. General Physician, Department of Paediatrics, Mosogar General Hospital, Ethiope West LGA, Delta State, Nigeria.

[c]. Neurology Registrar, Department of Internal Medicine, University of Nigeria Teaching Hospital, Ituku Ozalla,

Abstract:

Pain is conceptualized as multidimensional, unpleasant, emotional and sensory experience and a patient's response can vary widely based on physiologic, psychologic, and contextual factors (1). Bearing that in mind, chronic painful diabetic neuropathy is one of the most common complications of diabetes affecting half of the patients population (2). The first published description of pain in the setting of diabetes mellitus is more than 200 years old (3).

As observed by 4 Svokos et al that neuropathic pain consists of a complex, and chronic pain state that usually accompanied by tissue injury or damage. (4). In addition, Bridin 2018, however, is of the opinion that patients with escalating and poorly controlled diabetic neuropathy and erratic glycemic level worsens the symptoms and improving glycemic control may reduce the progression of painful neuropathy (5). This highlighted the pathophysiology though the origin of painful neuropathy in diabetics remains elusive (6). The current research is rapidly expanding the understanding of this conditions for a better management.

However, Bouhassira D et al and Papanas et al, observed that painful diabetic neuropathy involves smaller neuronal fibres and consist of distal symmetrical sensorimotor polyneuropathy (7, 8,9).

Smith et al and Aslam et al, are of the opinion that increased effect of hyperglycemia causes direct nervous and neuronal insults by increasing oxidative stress (10, 11), accumulation of advanced glycated end-products and improving axonal transport which by so doing impaired micro-vascular function due to its effects on endothelial function, leading to nervous hypoxia and ischemia (12). While Inoue et al opined that it is due to the excessive production of methyl glyoxal which causes hyperexcitability of the nociceptors receptors that occurs at the spinal ganglia which serves as the therapeutic target of pregabalin and gabapentin (13). Rapid glycemic control using insulin causing insulin neuritis and overall hyperexcitability of the sympathetic system in pain sensitization have been postulated as the enabling factors in inducing painful diabetic neuropathy (14).

Keywords; Painful Diabetic neuropathy, hyperglycemia, insulin neuritis, hyperexcitability

Introduction;

As described by IASP working Group and Raja et al; Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage (15, 16). Neuropathic pain caused by a lesion or disease of the somatosensory nervous system is a common chronic pain condition with major impact on quality of life (17); According to International Association of the Study of Pain (IASP),"Neuropathic pain is initiated or caused by a primary lesion or dysfunction of the nervous system, (17).

Also, It can result from damage anywhere along the neuraxis: peripheral nervous system, spinal or supraspinal nervous system (4).

However, painful diabetic neuropathy aetiopathogenesis has been linked to length-dependent axonopathy, primarily involving the distal portions of the longest myelinated and unmyelinated sensory axons. They tend to be relative sparing of the motor axons.(18,19); while the distal axonopathy is very common, proximal nerve dysfunction may also occur at the sensory ganglia (20).

Furthermore, ectopic activity in, for example, nerve-end neuroma, compressed nerves or nerve roots, dorsal root ganglia, and the thalamus may in different conditions underlie the spontaneous pain as seen in this condition (17). Evoked pain may spread to neighboring areas, and the underlying pathophysiology involves peripheral and central sensitization(17). Maladaptive structural changes and a number of cell-cell interactions and molecular signaling underlie the sensitization of nociceptive pathways(17). These include alteration in ion channels, activation of immune cells, glial-derived mediators, and epigenetic regulation (17). The major classes of therapeutics include drugs acting on α2δ subunits of calcium channels, sodium channels, and descending modulatory inhibitory pathways. (17).

Bearing that in mind, Painful diabetic peripheral neuropathy has been described as a superficial burning pain associated with other positive and/or negative sensory systems affecting the feet and lower extremities, (21). It is one of the most commonly encountered neuropathic pain syndromes in clinical practice. Presentation may be complicated by multiple symptoms, including allodynia, hyperalgesia, other less well characterized dysesthesias, and serious disruption of social functioning and mood of the patient (21). Peripheral nerve function may deteriorate, which can account for patient reports of diminution of pain after several years of follow-up (21). In addition, diffuse symmetrical distal sensorimotor neuropathy is the most common manifestation of this condition and is thought to affect up to 34% of all patients with diabetes (3). Age at diagnosis, duration of diabetes and poor glycemic control correlate with the presence of this condition (22). As with other neuropathic pain syndromes, presentation is often complicated by multiple symptoms, including allodynia, hyperalgesia and other less well characterized dysesthesias, and by serious disruption of social functioning and mood (23).

As a consequent, painful diabetic neuropathy management remains a therapeutic challenge for physicians and the patients (6). In this report, a case of painful diabetic neuropathy in the emergency setting is described.

Case Report;

A 57year old male patient who has been a type 2 Diabetes patient for 20years and has been on Glipzide and metformin presented to the emergency room with complaint of tingling, burning, shooting pains and numbness on the both feet. The pain was intermittent at onset but became persistent for the past 6months which prompted the patient to have visited several physicians and multiple hospital referrals. The pain was worst at night with no known aggravating and relieving factors. This prevented the patient from wearing his shoes. Patient denied any history of foot ulcers or swelling in any part of the his body and he rated the pain scale as 8 out of 10. His glycemic parameters at presentation was unrecordably “Hi” by the glucometer and Hb1AC was reported to be 8.5%. Examination findings showed a middle aged man in painful distress, His blood pressure is 138/90mmHg and his heart rate was 88. His cardiac and respiratory examination showed no abnormality. 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 was 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. Laboratory findings showed a moderate anemia (Hb 11.6g/dl), dipstick urinalysis showed glycosuria and negative nitrite level. While serum electrolyte and creatinine level showed sodium: 134mg/dl, Potassium: 4.0mg/dl, Calcium: 8g/dl, Creatinine: 2.5ug/l, BUN: 15
Bedside portable xray showed no abnormality on both feet. Nerve conduction studies showed no abnormality.

A diagnosis of chronic diabetic neuropathic pain with reduced quality of life was made and he was quickly placed on normal saline and insulin therapy 5iu with titration and intravenous paracetamol 1000mg at start dose but pain failed to stop. He was also given intravenous 5mg of pethidine diluted in 10mls of normal saline and pain started coming down. The glucose level went down to 200mg/dl after successive insulin therapy and he was subsequently placed on oral metformin and oral gabapentin with cobalamin and vitamin D supplementation and then counseled extensively to avoid missing his prescribed oral anti-diabetic agents and for referral to outpatient clinics (endocrinologist, orthopedic team, and nutritionist) and for further review and follow up.

Review of Literatures;

Clinical presentation of painful diabetic neuropathy at the emergency may be challenging that is why Bendow et al revealed that there is a tendency for diabetic patients who experience chronic pain to report a diminution in pain after several years of follow-up, a change that may parallel deterioration in peripheral nerve function (3). To clarify this unpleasant situation at the emergency setting; Svokos et al highlighted the need to differentiate neuropathic pain from other types of pain which include pain and sensory symptoms lasting beyond the healing period (4) that is to say beyond 3 months (24). It is characterized in humans by spontaneous pain, allodynia (the experience of non-noxious stimuli as painful), and causalgia (constant burning pain) (4). Spontaneous pain includes sensations of 'pins and needles,' shooting, burning, stabbing and paroxysmal pain (electric-shock like) often associated with dysesthesias and paresthesias, (25).

These sensations not only affect the patient's sensory system, but also the patient's well-being, mood, focus and thinking(4). In addition, neuropathic pain consists of both "negative" symptoms (sensory loss and numbness) and "positive" symptoms (paresthesias, spontaneous pain, increased sensation of pain). These have been observed in patients with cases of painful diabetic neuropathy (4)

A cross-sectional study done by Zakari et al among 300 diabetic outpatients at Morocco, found a prevalence of 15% of peripheral diabetic neuropathy and 74% of patients were under-diagnosed and under treated (6)

In a randomized controlled clinical trial as reported by Backonja M et al; they found that gabapentin monotherapy appears to be effective for the treatment of pain and sleep interferences associated with painful diabetic peripheral neuropathy and exhibits positive effects on mood and quality of life (26). Also, Gutierrez-Alvare et al, suggested that the use of anti-epileptic agents when used as analgesics in painful diabetic neuropathy remains controversal (27).

Furthermore, in this report, as revealed by Cheng et al, the only known means of slowing the progression of painful diabetic neuropathy is good glycemic control (28); In addition, the diabetes prevention program (DPP) looked at the effects of metformin versus aggressive diet and exercise counselling versus placebo and found that the diet and exercise arm was almost twice as effective (58% versus 31%) in reducing progressive risks to diabetes as the metformin group (29).

This poses a clinico-management challenge to clinicians because according to (30), there is no cure for painful diabetic neuropathy, however methods can be used to help ameliorate symptoms. The first step in the treatment is establishing optimal glucose control. Painful diabetic neuropathy 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, (30).

Medications can also be used to help decrease pain. Medications used in the treatment of the former include tricyclic antidepressants (TCA's), selective serotonin-norepinephrine reuptake inhibitors, calcium channel blockers—gabapentin and pregablin, opioids, local anesthesia, and topical agents (31) as well as the use of capsaicin (32). Anti-epileptic agents such as gabapentin and pregabalin have been linked with dizziness, somlence, peripheral oedema and weight gain (40), while opoids can cause opoid withdrawal crisis; tricyclic antidepressants have been linked with arrhythmias, constipation, precipitation of suicidal ideation and mood changes.

Other interventions as stipulated by Svokos et al include Invasive treatments which may be considered for patients with intractable painful neuropathy, (4). These treatments include epidural or perineural injections of local anesthetics or corticosteroids, implantation of epidural and intrathecal drug delivery systems, insertion of spinal cord stimulators, percutaneous electrical nerve stimulation, transcutaneous electrical nerve stimulation, acupuncture, exercise, cognitive behavioral therapy, graded motor imagery and supportive therapy transcutaneous electrical nerve stimulation (4), and neuromodulation (33). These approaches are reserved for patients with intractable chronic painful neuropathy who have failed conservative medical management and have undergone thorough psychological evaluation (4).

However, low vitamin D concentrations have been shown to be associated with painful diabetic neuropathy through microvascular injury or direct neuronal metabolic injury [34, 35) therefore multivitamin supplementation especially Vitamin E as revealed by Fatimah et al has been seen as having neuroprotective mechanism against oxidative neuronal damage (36). In addition to this,; Vitamin D also has a neuroprotective effect by regulating the VDR (vitamin D receptor) and L-type calcium channels [37] while Bell SHD 2012, observed that Vitamin D deficiency has been shown to be more common in diabetic patients who have symptoms of distal symmetrical polyneuropathy and also associated with a lower pain threshold which increased when the deficiency is corrected (38).

In Conclusion;

Chronic painful diabetic neuropathy causes more morbidity and poor quality of life among diabetic patients and the challenges in management thus remain an albatross. Even though efforts have been made in understanding the mechanism of this condition, the trial of medications have proved little or no benefit on management at the emergency setting. In this index report, patient's education, strict glycemic control as well as exercise (39) can help to slow disease progression and improve the quality of life.

Conflicts of Interest: None

Sponsorship or Inducement: None

REFERENCES

1. American College of Surgeons: ACS Trauma Quality Programs-best practices guidelines for acute pain management in trauma patients; 2020; 7

2. 5. Russell JW, Zilliox LA. Diabetic Neuropathies: continuum. Lifelong learning in neurology. 2014; 20(5): 1226-1240. PubMed | Google Scholar

3. Benbow SJ, Cossins L, MacFarlane A (1999). Painful diabetic neuropathy. Diabetic Med 16:632–644.

4. Svokos K, Goldstein L. The Pathophysiology of Neuropathic Pain. Pract Pain Manag. 2009;9(5)

5. Bridin PM: Neuropathic Pain; Current Definition and Review of Drug Treatment; Australian Prescriber 2018:41: 60-3; doi.org/10.18773/austprescr.2018.022

6. Zakaria C, Bouchra L, Sanae EH, Lahoussaine A, Said K, Hassan Q, Hicham B, Mohamed Z: The prevalence of painful diabetic neuropathy in 300 Moroccan diabetics, Pan African Medical Journal. 2018;31:158. doi:10.11604/pamj.2018.31.158.14687

7. 2. Bouhassira D, Letanoux M, Hartemann A. Chronic pain with neuropathic characteristics in diabetic patients: a French crosssectional study. PLoS One. 2013; 8(9): e74195. PubMed | Google Scholar

8. Papanas N, Vinik AI, Ziegler D. Neuropathy in prediabetes: does the clock start ticking early? Nat Rev Endocrinol. 2011 Jul 12;7(11):682-90. doi:10.1038/nrendo.2011.113. Review. PubMed PMID: 21750507.

9. Papanas N, Ziegler D. Prediabetic neuropathy: does it exist? Curr Diab Rep. 2012 Aug;12(4):376-83. Doi: 10.1007/s11892-012-0278-3. Review. PubMed PMID: 22562652

10. 5. Smith AG, Singleton JR. Impaired glucose tolerance and neuropathy. Neurologist. 2008 Jan;14(1):23-9. Doi: 10.1097/NRL.0b013e31815a3956. Review. PubMed PMID: 18195653.

11. 3. Aslam A, Singh J, Rajbhandari S. Pathogenesis of Painful Diabetic Neuropathy. Pain Re-search and treatment. 2014; 2014(4i):7. PubMed | Google Scholar

12. 10. Smith AG, Russell J, Feldman EL, Goldstein J, Peltier A, Smith S, Hamwi J, Pollari D, Bixby B, Howard J, Singleton JR. Lifestyle intervention for prediabetic neuropathy. Diabetes Care. 2006 Jun;29(6):1294-9. PubMed PMID:16732011.

13. 7. Inoue Y, Kimura A; Methylglyoxal and regulation of its metabolism in microorganisms. Advances in Microbial Physiology. 1995; 37: 177-227. PubMed | Google Scholar

14. 8. Herzberg U, Eliav E, Dorsey JM, Gracely RH, Kopin IJ. NGF involvement in pain induced by chronic constriction injury of the rat sciatic nerve. Neuroreport. 1997; 8(7):1613- 8. PubMed | Google Scholar

15. 232. IASP. IASP taxonomy. https://www.iasp-pain.org/terminology?navItemNumber=576. 2019

16. 399a.Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. In press. doi:10.1097/j.pain.0000000000001939

17. -Finnerup NB, Rohini K, Troels SJ: Neuropathic Pain: From Mechanisms to Treatment, Physiol Rev 101, 2021: 259-301

18. - 1. Malik RA. The pathology of human diabetic neuropathy. Diabetes. 1997; 46 Suppl 2: S50.

19. 2. Malik RA, Veves A, Walker D, Siddique I, Lye RH, Schady W, Boulton AJ. Sural nerve fiber pathology in diabetic patients with mild neuropathy: relationship to pain, quantitative sensory testing and peripheral nerve electrophysiology. Acta Neuropathol. 2001; 101(4): 367.

20. 3. Toth C, Brussee V, Cheng C, Zochodne DW. Diabetes mellitus and the sensory neuron. J neuropathol Exp Neurol. 2004; 63(6): 561.

21. Marchettini P, Teloni L, Formaglio F, Lacerenza M: Pain in diabetic neuropathy case study; Whole Patient management; European J of Neurology 2004, 11 (suppl.L): 12-21

22. Ziegler D, Gries FA, Spuler M, Lessmann F (1992). The epidemiology of diabetic neuropathy. Diabetic Cardiovascular Autonomic Neuropathy Multicenter Study Group. J Diabetes Complications 6:49–57.

23. Jensen PG, Larson JR (2001). Management of painful diabetic neuropathy. Drugs Aging 18:737–749.

24: British Pain Society: Guidelines for Pain Management Programmes for adults; An evidence-based review prepared on behalf of the British Pain Society, British Pain Society Pub, London, 2013:1-38; ISBN: 978-0-9561386-4-4

25. 1. International Association for the Study of Pain. Epidemiology of neuropathic pain: how common is neuropathic pain, and what is its impact? Washington: IASP; 2014. https://www.iasp-pain.org/Advocacy/Content.aspx?ItemNumber=3934 [cited 2018 May 1]

26. Backonja M, Beydoun A, Edward KR, Sherwyn S, Fonseca V, Hes M, Lamoreaux L, Garofalo E; Gabapentin for the Symptomatic Treatment of Painful Neuropathy in Patients with Diabetes Mellitus; A Randomized Controlled Trials; Jama 1998; 280(21): 1831-1836

27. Gutierrez-Alvarez AM, Beltran- Rodriguez J, Moreno CB; Anti-epileptic Drugs in Treatment of Pain caused by Diabetic Neuropathy; Journal of Pain and Symptom Management, 2017, 34(2):201-207.-

28.-Cheng, M, Cheng ET; A Case Report: Idiopathic Peripheral Neuropathy Preceding Frank Diabetes by Seven Years; Proceedings of UCLA Healthcare-VOLUME 18 (2014): 1-3

29. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002

30. 4. The effect of intensive diabetes therapy on the development and progression of neuropathy. The Diabetes Control and Complications Trial Research Group. Ann Int Med. 2003; 163: 2433-2445.

31. Karen W, Richard F, Thomas AP; Lippincolt Illustrated Reviews Pharmacology; Wolters Kluwer Pub; 2015; 6ed (pg135-204).

32. 20.-Capsaicin Study Group (1991). Treatment of painful diabetic neuropathy with topical capsaicin. A multicenter, doubleblind, vehicle-controlled study. Arch Intern Med 151:2225–2229.

33. 14. Dworkin RH, O'Connor AB, Kent J, Mackey SC, Raja SN, Stacey BR, et al. Interventional management of neuropathic pain: NeuPSIG recommendations. Pain 2013;154:2249-61. https://doi.org/10.1016/j.pain.2013.06.004

34. - 5. Qu GB, Wang LL, Tang X et al. The association between vitamin D level and diabetic peripheral neuropathy in patients with type 2 diabetes mellitus: An update systematic review and meta analysis. J Clin Transl Endocrinol [Internet]. 2017;9:25–31.

35. 6. Oraby MI, Srie MA, Abdelshafy S, Elfar E. Diabetic peripheral neuropathy: The potential role of vitamin d deficiency. Egypt J Neurol Psychiatry Neurosurg. 2019;55(1):1–8

36. -Fatima I, Naima B, Jehanna A, Kaoutar EA, Wafa R, El Hachmia AB, Ahmed B, Ali B, Mohamed Y: Vitamin E in ataxia and neurodegenerative diseases; A review: World Journal of Neuroscience,2012,2;217-222; http; dx.doi.org/10.4236/wjns.2012.24033

37. 4. Wei W, Zhang Y, Chen R et al. The efficacy of vitamin D supplementation on painful diabetic neuropathy: Protocol for asystematic review and meta-analysis. Medicine (Baltimore) 2020;99(31):e20871.

38. Bell SDH: Case Report; Reversal of the Symptoms of Diabetic Neuropathy through Correction of Vitamin D Deficiency in a Type 1 Diabetic Patient; Hindawi Publishing Corporation Case Reports in Endocrinology, Volume 2012, Article ID; 165056, 3 pages; doi:10.1155/2012/165056

39. Hong J; Whole Body Vibration Therapy for Diabetic Peripheral Neuropathic Pain: Health Sci J, 2011; 5(1), 67 pp:66-71 E-ISSN:1791-809X

40. Tan GLC, Rosales RL; Two much Pain: A Patient with Painful Diabetic Neuropathy and Post Herpetic Neuralgia, a Case Report and Review: *Diabetes Manag* (2016) 6(2), 051–054; ISSN 1758-1907