Diabetic neuropathy and painful diabetic neuropathy: Cinderella complications in South East Asia

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Abstract

The most common and debilitating microvascular complication of diabetes is diabetic peripheral neuropathy (DPN), affecting 50-90% of people with diabetes. The major manifestations of DPN are painful (pDPN) and painless diabetic peripheral neuropathy. Painful symptoms, occur in the feet and are worse at night and whilst they alert both the patient and physician, are often misdiagnosed and mismanaged. The devastating presentation of painless neuropathy with loss of sensation is foot ulceration and Charcot foot. The explosion of diabetes, especially in the South East Asian (SEA) region will result in an increasing prevalence of both painful and painless diabetic peripheral neuropathy. PubMed, EMBASE, Medline and Google Scholar databases were searched between 1990 and 2017. This highlights the widely varying prevalence of DPN and pDPN in the World Health Organization (WHO) defined SEA countries and the dearth of published studies, especially in pDPN. We believe this will provide new direction for future research on DPN in the SEA region.

Keywords: Diabetes, Diabetic neuropathy, Painful diabetic neuropathy, South East Asia.

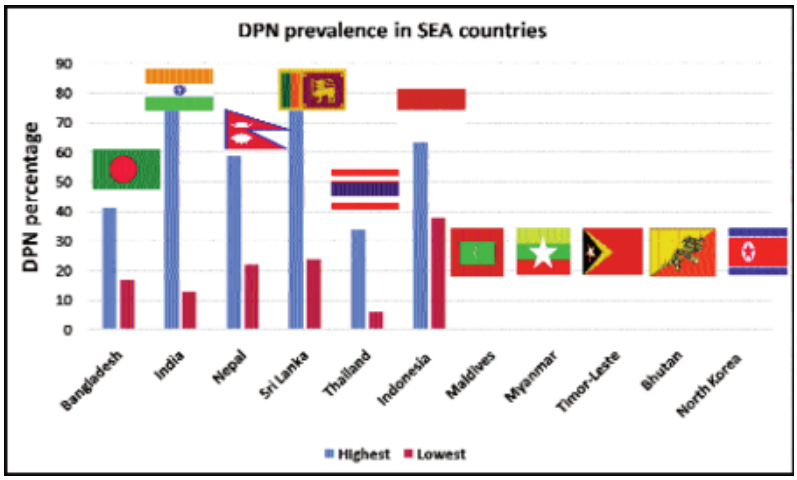

Figure-1: The highest and lowest prevalence of DPN reported in each country from SEA including countries where there are no published data.

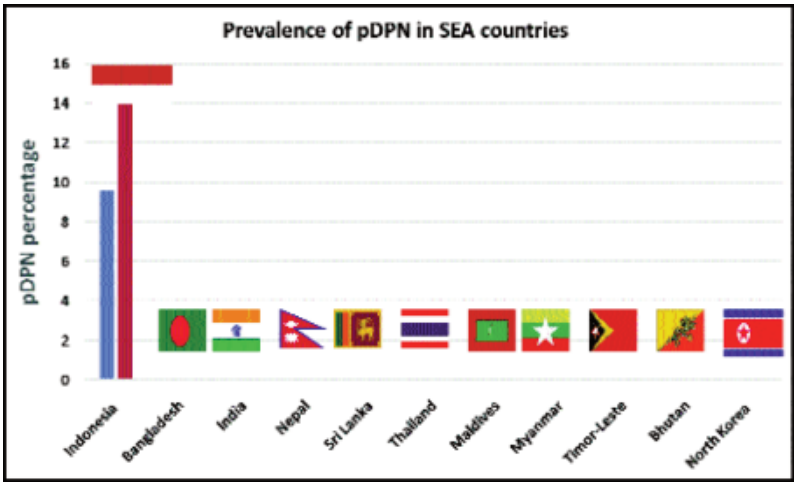

Figure-2: The highest and lowest prevalence of pDPN reported in each country from SEA, including countries where there are no published data.

Introduction

The eleven SEA countries (Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Indonesia, Maldives, Myanmar, Nepal, Sri Lanka, Thailand, and Timor-Leste) are undergoing rapid urbanization with a major impact on the diet and lifestyle of this population. Accordingly, the international Diabetes Federation has predicted that the number of people with diabetes in this region, which was 71.4 million in 2011, will increase to 120.9 million by 2030.[1] This explosion of diabetes will inevitably be followed by an increased prevalence in the long-term complications, which are costly to both the individual and society. We have undertaken a review of the literature (PubMed, Google Scholar, Embase and Medline) from 1990-2017 on

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neuropathy, 'the Cinderella complication' of diabetes. This highlights the disparity in the prevalence of published data on both DPN (Figure-1) and pDPN (Figure-2) in the SEA region.

Diabetic peripheral neuropathy

Bangladesh

In a small cross-sectional study in 2006 in the outpatient department of BIRDEM Hospital, a tertiary care centre in Dhaka, 294 randomly selected patients with Type 2 Diabetes Mellitus (T2DM) aged 50.8±10.6 years underwent assessment with the Neuropathy Symptom Score (NSS) and Neuropathy Disability score (NDS). The prevalence of DPN was 19.7% and increased with age and duration of diabetes.[2] In a study from 2012 in the outpatient department of a tertiary care hospital the prevalence of DPN was 35%. This was a cross-sectional study of 140, predominantly T2DM patients aged 53.2±10.5 years and diabetes duration 6.3 ± 5.6 years. The diagnosis of DPN was based on a local questionnaire and patient interview.[3] In another study of 400 patients, neuropathy was diagnosed from the medical records and a prevalence of 16.8% was established.[4] In a study of 1860 patients with T2DM, the medical records were reviewed and the prevalence of neuropathy symptom, absent ankle jerk, and leg amputation were 31.7%, 41.1% and 1.2%, respectively.[5]

India

In 2013 a cross sectional study was undertaken in an outpatient clinic in a public tertiary care hospital in North India in 586 participants of whom 18.4% were newly diagnosed (< 6 months) and 81.6% had known diabetes with a mean age of 57.1±9.7 years and mean duration of diabetes of 10.8±7.5 years. Insensitivity to the Semmes-Weinstein monofilament (SWM), pinprick sensation and absence of ankle reflexes and vibration perception threshold (VPT) were used to define DPN. The prevalence of DPN in those with known diabetes and newly diagnosed diabetes was 33.7% and 9.2%, respectively.[6] In a study from south India, 1000 diabetic patients underwent biothesiometry and assessment of VPT on the great toes. AVPT cut-off of 25 volts was used to diagnose 'neuropathy', which was found in 19.1%.[7] Of course, this indicates patients 'at risk of foot ulceration' and not neuropathy. A retrospective study from Goa Medical College reviewed records of 3261 patients with T2DM and defined peripheral neuropathy from a history of pain, tingling, and numbness and established a prevalence of 16.3%.[8] In another study of 1500 patients with young onset diabetes aged 34.68±4.23 years, the prevalence of advanced neuropathy, based on absent SWM, 128 Hz tuning fork, and a VPT ≥20 V on the great toes was found to be 13.1%.[9] In a study of 195 T2DM patients with newly diagnosed T2DM using the NSS and NDS to diagnose DPN the prevalence was found to be 29.2%.[10] One study screened 4600 patients, within 3 months of being diagnosed with T2DM using an absence of sensation to the 128 Hz tuning fork, SWM, loss of ankle reflexes and the Michigan neuropathy screening instrument (MNSI) and established a prevalence of 13.13%.[11] In a study of 208 patients with T2DM the DPN prevalence was found to be 18.3% using the MNSI history and 32.2% using the neurological exam.[12] In a study from Northwest India 11,157 patients with T2DM underwent assessment with the SWM, VPT, and ankle reflexes to diagnose DPN and established a prevalence of 26.8%.[13] In a study of 1783 T2DM patients undergoing regular follow up compared to 1798 T2DM patients with irregular follow-up, neuropathy based on a VPT on the great toes of ≥20 V was found in 14.1% and 12.8%, respectively.[14] A small study utilized monofilament insensitivity to assess neuropathy in 105 T2DM patients in a tertiary care centre and found a prevalence of 77.1%, clearly indicating referral bias.[15] In a study of 100 newly diagnosed T2DM patients where neuropathy was diagnosed from symptoms of numbness and tingling and monofilament insensitivity, the prevalence was found to be 16%,[16] whilst in another study of 105 newly diagnosed T2DM patients from a rural area, neuropathy diagnosed by insensitivity to the monofilament, 128Hz tuning fork, and absent ankle reflexes established a prevalence of 23%.[17] In a retrospective study of 249 T2DM patients in a tertiary setting, a surprisingly low prevalence of 14.4% was established, but the method of diagnosing neuropathy was not disclosed.[18] In a study of 1266 individuals, the prevalence of diabetes was found to be 10.3% and of these patients with diabetes, 40% were found to have bilateral loss of ankle reflexes and distal sensory loss.[19] In a study of 42 villages from the state of Tamil Nadu, of 23,380 individuals, in 1001 patients with diabetes a prevalence of 30.9% was established based on a VPT cut-off of ≥20V.[20] Hundred newly diagnosed patients with T2DM were assessed for neuropathy using NSS, NDS and nerve conduction studies and were diagnosed with neuropathy when two or more of these measures were abnormal to establish a prevalence of 29%.[21] In a sample of 1319 T2DM patients from 4 centers across India, SWM insensitivity was found in 15%.[22] Based on a VPT of ≥20V in a study from Northern India of 102 patients with T2DM, 60.7% were abnormal,[23] whilst in a study from South India in a sample of 1291 with known diabetes and 338 patients with newly diagnosed diabetes the prevalence of neuropathy was 27.8% and 19.5%,

respectively.[24] In another study of 283 T2DM patients using NSS and NDS a prevalence of 33.33% was established[25] and a study of 212 diabetic patients using the MNSI established a neuropathy prevalence of 47%.[26]

Nepal

In a cross-sectional study at Kathmandu Medical College Teaching Hospital, and Temple of Healing clinic, 271 diabetic patients underwent biothesiometry and VPT was assessed at six different sites on the sole of each foot. A diagnosis of neuropathy was correctly made if the VPT exceeded 15 volts and this established a prevalence of diabetic sensory neuropathy of 58.7%.[27] In a 2010 hospital based study of 100 diabetic patients attending an outpatient clinic in Dharan, the prevalence of DPN was 44.4% based on SWM insensitivity and loss of ankle reflexes.[28] In a cross-sectional study from 2013, 306 older participants from 2 rural and 2 urban areas with a median age of 71 years, underwent a neurological examination to establish a prevalence of DPN of 22.2%.[29] In a study of 157 patients with T2DM, the prevalence of symptomatic neuropathy was found to be 32.5%.[30]

Sri Lanka

A cross-sectional study of 528 diabetic patients (191 newly diagnosed) used the Diabetic Neuropathy Symptom (DNS) score to establish a DPN prevalence of 48.1%. They further used the Toronto Clinical Scoring System (TCSS) in those with known diabetes and found a prevalence of 24%.[31] A more recent study from the Diabetic center in Jaffna was undertaken in 8401 diabetic patients and using the SWM and biothesiometer, established a DPN prevalence of 34.1%.[32] In a study of 597 newly diagnosed diabetic patients in primary care an abnormal NSS or NDS and VPT established a DPN prevalence of 25.1%,[33] whilst using the same criteria in 500 diabetic patients from a diabetic clinic in the general hospital of Colombo, the DPN prevalence was found to be 30.6%.[34] In a study of 344 patients the prevalence of DPN established using the TCSS was found to be 30.4%.[35] In a recent study of 235 patients with T2DM in a tertiary hospital based clinic, DPN was diagnosed in 74%, based on an abnormal DN4 questionnaire and insensitivity to SWM and vibration and joint position.[36] In a study of 384 subjects with T2DM DPN was diagnosed based on an abnormal MNSI, Diabetic Neuropathy Index (DNI) and monofilament test and showed a prevalence of 45.6%.[37] In a study of 1007 young diabetic patients aged 36.6±11.17 years with a diabetes duration of 4.8±4.2 years, using neurological symptoms and signs and the DNS score the prevalence of DPN was found to be 30.7% and amongst these patients insensitivity to the monofilament, vibration sense, and absence of ankle jerks was found to be 7.5%, 7.2% and 4.2%, respectively.[38]

Thailand

A retrospective study of 1110 (T1DM-6%, T2DM- 94%) diabetic patients from 37 primary health care clinics in an urban setting found a DPN prevalence of 34%.[39] Whilst in a cross-sectional study from seven public hospitals, 899 Thai T2DM patients underwent assessment with the SWM on seven areas of the foot and 15.9% were diagnosed with advanced neuropathy and deemed at high risk of foot ulceration.[40] In a study of 608 T2DM patients, 16.8% were diagnosed with DPN based on an abnormal Achilles tendon reflex and sensitivity to SWM and vibration sensation at the hallux.[41] A study comparing medical records in 383 patients from the Siriraj Continuity of Care clinic and in 374 patients from the outpatient clinic, established a prevalence 9.7% and 2.9%, respectively.[42] In a cross-sectional study of 438 diabetic patients from a tertiary care diabetes clinic, insensitivity to the SWM was found in 19.2%.[43]

Indonesia

In a cross-sectional study undertaken between 2008-2009, in 1785 individuals the prevalence of DPN was found to be 63.5%, with symptoms being present in 67.1% and absent ankle jerks in 67.7% of patients.[44] A retrospective study from Surabaya assessed the medical records of 302 T2DM patients and found the prevalence of DPN to be 58.6%.[45] In a study of a 155 outpatients from the Cipto Mangunkusumo Hospital the prevalence of neuropathy (symptoms and signs in hospital records) was 38%.[46]

Painful diabetic neuropathy

The studies on painful diabetic neuropathy from the SEA region are very limited. A large study from 13 neurology outpatient clinics from Indonesia used the DN4 and Leeds Assessment of Neuropathic Symptoms and Signs score (S-LANSS) in 8160 subjects. 1,779 patients reported neuropathic pain: 9.6% were attributed to diabetic neuropathy, 28.6% to back pain, 19.3% to carpal tunnel syndrome, 10.7% to frozen shoulder syndrome and 6.1% to brachialgia.[47] In a study of 84 patients with diabetes who underwent assessment with a structured questionnaire, pDPN was diagnosed in 14.3%.[48] Indeed, the limited studies and awareness of pDPN may well explain the findings of our recent study showing important differences between physician and patient perceptions of pDPN in Hong Kong, Malaysia, the Philippines, Taiwan, and Thailand, with major repercussions on the diagnosis and treatment of this condition.[49]

Future Directions

Although there is a reasonable literature on the prevalence of diabetic peripheral neuropathy in some of the SEA countries there are no published data from Bhutan, Democratic People's Republic of Korea, Maldives, Myanmar, and Timor-Leste. Even the published data has been derived from small studies in tertiary care centers, often using non-validated instruments. Because the methods of ascertaining neuropathy are highly variable the prevalence ranges from as little as 2.7% to 83.4%, depending on whether medical records or neurophysiology were used to diagnose DPN. The majority of studies rely on 10g-monofilament insensitivity to diagnose 'neuropathy' when they are actually diagnosing patients with severe neuropathy and the 'at risk foot'. Alarmingly there are no published data on the prevalence of painful diabetic neuropathy in the majority of countries including surprisingly, India and Sri Lanka. If diabetic neuropathy and painful diabetic neuropathy are to be adequately addressed, there must be a concerted effort to establish population based prevalence figures to guide health care providers, governments and international agencies such as the WHO to establish policies which will optimally deal with this Cinderella complication of diabetes. Once the true prevalence figures are established we can identify the risk factors and optimal treatments in relation to the type and dose of drugs, which will be most beneficial for patients with DPN in this region. All the current guidelines are based on studies from Europe and North America, where optimal treatment strategies may not necessarily be applicable to patients in the SEA region.[50]

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