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REVIEW ARTICLE

Diagnosing peripheral neuropathy in South-East Asia: A focus on diabetic neuropathy

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ABSTRACT

Burning and stabbing pain in the feet and lower limbs can have a significant impact on the activities of daily living, including walking, climbing stairs and sleeping. Peripheral neuropathy in particular is often misdiagnosed or underdiagnosed because of a lack of awareness amongst both patients and physicians. Furthermore, crude screening tools, such as the 10-g monofilament, only detect advanced neuropathy and a normal test will lead to false reassurance of those with small fiber mediated painful neuropathy. The underestimation of peripheral neuropathy is highly prevalent in the South-East Asia region due to a lack of consensus guidance on routine screening and diagnostic pathways. Although neuropathy as a result of diabetes is the most common cause in the region, other causes due to infections (human immunodeficiency virus, hepatitis B or C virus), chronic inflammatory demyelinating polyneuropathy, drug-induced neuropathy (cancer chemotherapy, antiretrovirals and antituberculous drugs) and vitamin deficiencies (vitamin B_1, B_6, B_{12}, D) should be actively excluded.

INTRODUCTION

Burning pain in the feet and lower limbs can have a significant impact on the activities of daily living, including walking, climbing stairs and sleeping. It is a common presenting complaint to primary care physicians. The differential diagnosis of such pain includes inflammatory, musculoskeletal and neuropathic causes. Peripheral neuropathy (PN) is often misdiagnosed or underdiagnosed due to a lack of awareness amongst both patients and physicians. The use of crude screening tools, such as the 10-g monofilament, which only detects advanced large fiber neuropathy, contributes to delayed diagnosis. Furthermore, the underestimation of PN is especially prevalent in the South-East Asia (SEA) region due to a lack of consensus guidance on routine screening, diagnosis and management[1].

PERIPHERAL NEUROPATHY IN SEA

Peripheral neuropathy in SEA is associated with multiple possible causes, such as metabolic disease (particularly diabetes mellitus), infections (human immunodeficiency virus [HIV] and hepatitis B or C virus), chronic inflammatory demyelinating polyneuropathy[2], drug-induced toxicity (cancer chemotherapy, antiretrovirals and antituberculous drugs) and vitamin deficiencies (vitamin B_1, B_6, B_{12}, D)[3]. The causes of PN in these countries might also differ from rural to urban areas; for example, in the Philippines and India, workers in the agricultural sector are exposed to organophosphorus pesticides, which can lead to PN[4]. Tuberculosis (TB) remains a major public health concern in SEA, contributing to 40% of the global burden of disease, and the increasing incidence of HIV increases the risk of TB. TB is associated with PN, and antituberculous drugs, especially isoniazid, can lead to PN[5]. In addition, with drug-resistant TB, various second-line treatments, such as cycloserine, ethionamide, fluoroquinolones and newer drugs (such as linezolid), can cause PN (26%)[6]. HIV is associated with PN[7], and the concomitant treatment of HIV and multidrug resistant-TB can result in PN in ~50% of patients[8]. Long-term survivors of childhood acute lymphoblastic leukemia can have a high prevalence of PN and in a Malaysian series of 101 acute

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lymphoblastic leukemia survivors treated with vincristine, 26.7% had an abnormal clinical Total Neuropathy Score, and 68.3% had electrophysiological evidence of neuropathy[9]. In a study of 150 consecutive patients with systemic lupus erythematosus from Malaysia, 15.3% had polyneuropathy characterized by numbness, tingling and pain, with a predominantly axonal neuropathy on electrophysiology[10]. In East Asia, Guillain–Barré syndrome might be particularly troublesome in relation to anti-ganglioside antibodies and acute motor axonal neuropathy[11].

DIABETIC PERIPHERAL NEUROPATHY

There are limited published data on the prevalence of diabetic neuropathy (Figure 1), particularly painful diabetic neuropathy in the SEA region[12]. In 1998, the Diabcare-Asia study of 22,177 patients in 230 diabetes centers across 12 Asian regions showed that the prevalence of diabetic neuropathy, as recorded in the medical records, was 29% in patients with type 1 diabetes and 35% in those with type 2 diabetes[13]. More recently, a global, prospective observational study of 15,992 patients with type 2 diabetes emphasized the higher prevalence of neuropathy (7.7%) compared with albuminuria (4.3%)[14].

Singapore

In a case–control study of 55 patients with type 2 diabetes in primary care, 32.7% experienced spontaneous pain, 12.7% had painful paresthesia and 34.6% had absent tendon reflexes[15].

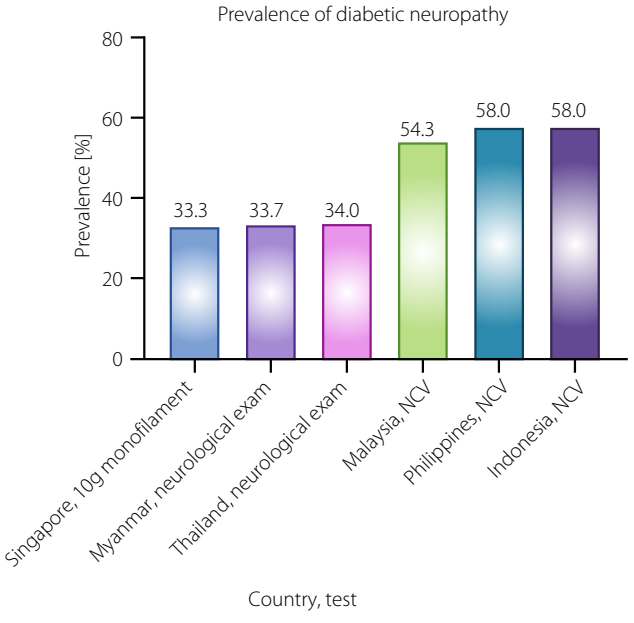

Figure 1 | Prevalence of diabetic neuropathy in different South-East Asian countries, confirmed with the specified tests. Data shown for Singapore (Nather 2010[16]), Myanmar (Win 2019[32]), Thailand (Nitiyanant 2007[31]), Malaysia (Abougalambou 2012[22]), the Philippines (Dagang 2016[26]) and Indonesia (Fitri 2019[28]). No data available for Vietnam, Cambodia, Brunei and Laos. NCV, nerve conduction velocity.

Whereas a study of 2,137 type 1 and 2 diabetes mellitus patients from a single tertiary hospital identified advanced neuropathy in 33.3% of patients using 10-g monofilament testing and in 39.5% of patients using Neurothesiometer testing[16]. A nationwide Singapore National Healthcare Group Diabetes Registry corroborates the steadily increasing prevalence of lower limb complications (International Classification of Diseases, Ninth Revision, Clinical Modification codes – dermopathy, peripheral vascular disease and neuropathy) in type 2 diabetes mellitus patients between 2005 (n = 129,183) and 2008 (n = 170,513) in both primary care (3.0–5.3%) and specialist (13.2–23.8%) clinics[17]. A recent study compared 8,150 patients with diabetes mellitus who underwent foot screening with 8,150 patients who did not, and showed that the risk of both minor (3.5-fold) and major (25-fold) amputation was significantly increased in the latter, emphasizing the importance of screening for DPN[18]. In two separate studies from Singapore, the presence of DPN has been associated with a poorer functional status and health-related quality of life[19,20].

Malaysia

In 138 patients admitted with diabetic foot ulceration or minor amputation, not surprisingly there was an association with loss of sensitivity to the 10-g monofilament[21]. In a university hospital clinic in Malaysia, of 1,077 patients with type 2 diabetes, 54.3% had abnormal nerve conduction studies[22]. In a study of 438 patients from private primary care clinics, neuropathy (30.1%) was the most common long-term complication followed by retinopathy (23.5%) and albuminuria (22.9%)[23]. In a study of 134 diabetes patients attending a primary care clinic in Kuala Lumpur, the prevalence of diabetic neuropathy based on the Neuropathy Symptom Score and Neuropathy Disability Score was 50.7%[24].

The Philippines

A study from the Philippines in 2000 from the Diabcare-Asia project, which assessed 2,708 patients in diabetes centers, reported a prevalence of 42% for diabetic neuropathy, based on medical records[25]. A more recent study of 150 diabetes patients at the Philippine General Hospital showed a DPN prevalence of 58%, based on an abnormality in nerve conduction studies[26].

Indonesia

In a study from Bali, of 110 patients with type 2 diabetes mellitus and neuropathy based on electromyography, 54% had painful diabetic neuropathy[27]. In a recent study of 50 patients with diabetes attending a hospital clinic in Medan, 58% had abnormalities on nerve conduction testing[28].

Thailand

A nationwide cross-sectional study of 30,423 diabetes patients attending public hospitals across Thailand found a prevalence of 3.1% for PN; however, this was based on International Classification of Diseases, 10th Revision coding[29]. Indeed, in a study

of 608 diabetes patients attending a hospital clinic, 16.8% had advanced diabetic neuropathy based on loss of ankle reflexes, vibration perception and insensitivity to the 10-g monofilament[30], whereas the prevalence of diabetic neuropathy in 1,078 diabetes patients attending primary care was 34%[31].

Myanmar

In a recent study of 975 participants with type 2 diabetes mellitus attending outpatient clinics in four hospitals in Myanmar, 33.7% had neuropathy, of whom 59.5% had painful neuropathy[32].

Vietnam

A study in 71 patients with diabetes identified a high prevalence (68%) of mild cardiac autonomic dysfunction, of whom 52% had at least two abnormal heart rate variability tests[33].

Cambodia, Brunei, Laos, Vietnam

There are no English language published data on the prevalence of diabetic neuropathy from Cambodia, Brunei, Laos or Vietnam.

CHALLENGES IN DIAGNOSING DPN IN PRIMARY CARE

There is a lack of awareness and urgency in making the diagnosis of DPN, even though advanced DPN with foot ulceration[34] and especially amputation[35] is associated with a 5-year mortality that exceeds that of patients with a previous myocardial infarction, stroke[36] and other microvascular complications, such as hemodialysis for end-stage renal disease[37] and vitrectomy for proliferative diabetic retinopathy (Figure 2)[38]. Indeed, the perception of most physicians who see patients with diabetes is that cardiovascular disease, retinopathy and nephropathy can be managed effectively, whereas "nothing can be done" for DPN.

CHALLENGES WITH CURRENT RECOMMENDED DIAGNOSTIC TOOLS

Several diagnostic screening questionnaires, such as the McGill Pain Questionnaire, NeuroQoL and Neuropathy Symptom Score, which rely on the patient's reported clinical symptoms have been used. Screening tools that assess both clinical signs and symptoms include the Neuropathy Disability Score, Michigan Neuropathy Screening Instrument and Douleur Neuropathique 4, and were initially validated in studies in Western populations and written in the English language. These tests have been translated and validated in many other languages, and are widely available, but remain woefully underutilized.

The tools recommended and most commonly used today for screening and diagnosing PN are the monofilament test, ankle reflex and vibration perception testing using a 128-Hz tuning fork. The challenge in most countries is that even these simple diagnostic tools are only available in a specialist setting. Foot examinations are usually cursory only if patients report symptoms. Monofilament testing detects moderate-to-severe PN, and

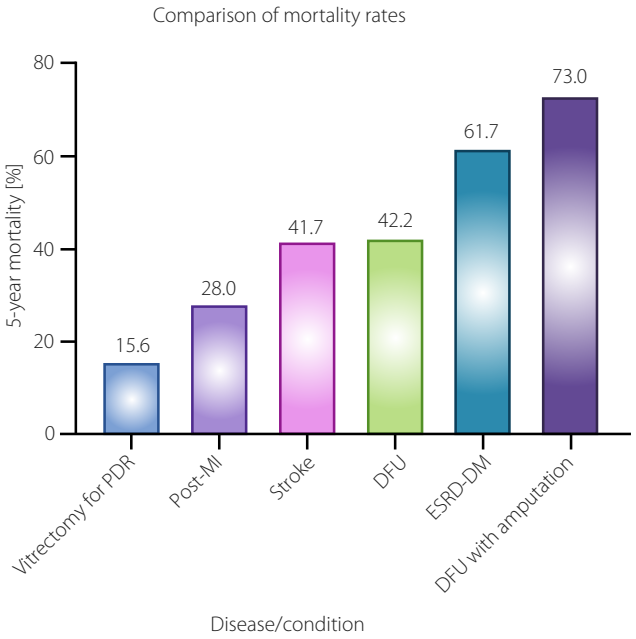

Figure 2 | Comparison of 5-year mortality rates in patients after myocardial infarction (MI) and stroke (Malik 2016[36]), vitrectomy for proliferative diabetic retinopathy (PDR; Liu 2019[38]), diabetic foot ulceration (DFU; Walsh 2016[34]), end-stage renal disease in diabetes mellitus (ESRD-DM; Lu 2017[37]) and DFU with amputation (Apelqvist 1993[35]).

even this is not available in most SEA countries in primary care and indeed most primary care physicians do not know how to carry out the test. Objective diagnostic tests of PN can be undertaken by neurophysiologists to evaluate nerve conduction velocity, amplitude and F-wave latency to identify different causes of neuropathy, and differentiate chronic inflammatory demyelinating polyneuropathy from DPN and so on[39]. Skin biopsy[40] and corneal confocal microscopy[41,42] can also be used to objectively quantify early small fiber neuropathy, but require expertise to carry out and are currently not feasible in primary healthcare. However, more recently, easy to use devices, such the DPN-Check and Sudoscan, have become available to allow non-specialists to identify large and small fiber neuropathy[43].

RECOMMENDATION FOR THE DIAGNOSIS OF PERIPHERAL NEUROPATHY IN SEA

In a survey of physician and patient perceptions of painful DPN, we identified that the physician–patient dialogue was central to increasing the awareness of the complications of PN and overcoming the burden of this disease[1]. A first critical step is to increase patients' awareness of PN and a sense of urgency to seek medical consultation. Other than knowledge about the condition, information on who is at risk, the consequences of PN in relation to reduced quality of life and increased risk of foot ulcers needs to be disseminated to the public, to encourage early self-referral[44]. Once the diagnosis of PN has been made, it

Table 1 | Simple diagnostic procedure for peripheral neuropathy in patients presenting with neuropathic symptoms

Recommendation for the diagnosis of PN
Step 1: Classification into acute, subacute and chronic
Step 2: Medical history
Step 3: Assessment of symptoms of peripheral neuropathy
Step 4: Neurological examination
Step 5: Laboratory tests to support or refute the diagnosis of PN

PN, peripheral neuropathy.

is important to educate patients of the dangers of PN. A recent systematic review has found that health education programs increase the foot self-care scores and reduce foot problems[45]. Furthermore, to increase awareness among physicians, more data need to be gathered and published on the prevalence of DPN from the region[12]. It is also important that governments in the region attempt to harmonize their guidelines with other international guidelines. Indeed a recent analysis showed that six national guidelines of Western Pacific nations were at best only partially similar to 53% of the recommendations by the International Working Group on the Diabetic Foot; specifically 42% for wound healing, 40% for infection, 40% for peripheral artery disease and just 20% for offloading[46].

PRACTICAL STEPPED APPROACH TO THE DIAGNOSIS OF PERIPHERAL NEUROPATH

Given the existing limitations within primary healthcare in SEA, an easy, fast and reliable diagnostic procedure is required (Table 1). It should be a simple and systematic approach to enable allied health staff to assess the majority (~90%) of patients, especially in countries with geographical challenges, such as Indonesia and the Philippines.

Step 1. Classification into acute, subacute and chronic

A simple classification based on the onset of symptoms will provide an initial differential diagnosis. Generally, if the symptoms are chronic, the physician should consider diabetic or hereditary neuropathy; subacute, consider inflammatory, immune-mediated, metabolic (diabetes, nutritional deficiency), medication or chemotherapy, whereas acute onset could be due to an infectious cause (Guillain–Barré syndrome) or a toxin (Table 2).

Step 2. Careful medical history

Underlying causes of PN can be identified by taking a careful medical history alongside simple laboratory tests. However, of all patients with PN, 24–27% will have idiopathic neuropathy where no underlying cause can be identified[47]. In patients with diabetes, it is important to exclude other causes of PN (Table 3).

Step 3. Assessment of symptoms and signs of peripheral neuropathy

The history taking should be proactive and should focus on four or five main characteristics of PN such as numbness, pins and needles, and tingling sensation, lancinating stabbing or electric shock-like pain[48]. Acknowledging that it might be difficult for the patient to express symptoms or for the physician to translate these words into the exact local language, the algorithm could include simple descriptions/descriptive questions that can be used by physicians. Examples can help the patient to visualize or imagine a symptom; for example "Do you have a feeling as if ants are crawling along your feet?", "Does it feel like electric shocks from nothing?", "Does a touch of the bedsheet on your feet sometimes feel painful?" Other questions to be included should elicit more details about the localization or the course of symptoms; for example, "Where is the pain/sensation experienced?", "Does it occur on both sides (symmetrical)?", "Is it worse at night?"

Alternatively, simple questionnaires, such as the Douleur Neuropathique 4, can be used to differentiate neuropathic pain from nociceptive pain based on seven interview questions, assessment of hypoesthesia to touch and pinprick, and the presence of allodynia[49,50].

Table 2 | Classification of peripheral neuropathy based on clinical progression

Acute (days)	Subacute (weeks to months)	Chronic (>6 months)	Relapsing–remitting
Guillain–Barré syndrome	Nutritional deficiency	Hereditary neuropathy	Guillain–Barré syndrome
Acute intermittent porphyria	Prolonged exposure to toxin	Diabetic neuropathy	Porphyria
Diphtheria	Metabolic (diabetic neuropathy, uremic neuropathy)	CIDP	CIDP
Thallium/mercury/arsenic/ lead toxicity	Immune-mediated (e.g., CIDP, vasculitis, sarcoidosis)	Hereditary (e.g., Charcot–Marie–Tooth, familial amyloidosis) HIV neuropathy	HIV/AIDS
Critical illness neuropathy	Neoplastic (e.g., hematological/ lymphoproliferative malignancies)	CIPN	
	Paraneoplastic (e.g., anti-Hu)		

CIDP, chronic inflammatory demyelinating polyneuropathy; CIPN, chemotherapy-induced peripheral neuropathy; HIV, human immunodeficiency virus; PN, peripheral neuropathy.

Table 3 | Other causes of peripheral neuropathy based on a careful history, clinical examination and laboratory investigations

Metabolic disease	Hypothyroidism
	Chronic liver disease
	Chronic kidney disease
	Prediabetes
	Prediabetes
Systemic disease	Systemic/non-systemic vasculitis (ANCA, cryoglobulinemia)
	Paraproteinemia
	Amyloidosis
Infectious	HIV
	Leprosy
	Hepatitis B/C
Inflammatory	Chronic Inflammatory demyelinating polyneuropathy
Nutritional	Vitamin B deficiency (B_{12}, B_1, B_6)
	Malabsorption syndromes
	Bariatric surgery
Toxins	Organophosphorus agents
	Alcohol
	Arsenic
	Mercury
Medication	Isoniazid
	Colchicine
	Dapsone
	Amiodarone
	Nitrofurantoin
	Metronidazole
	Ethambutol
	Chemotherapy (vincristine, cisplatin, Taxol, bortezomib)

ANCA, anti-neutrophil cytoplasmic antibodies; CIDP, chronic inflammatory demyelinating neuropathy; HIV, human immunodeficiency virus; PN, peripheral neuropathy.

Step 4. Neurological examination

A neurological examination using simple tools should be established as a routine in primary care, and should include vibration perception testing using a 128-Hz tuning fork, pin-prick test and temperature sensation testing alongside reflexes. In a study from Singapore of 60 patients without diabetic foot problems, the simple pin-prick test identified a greater proportion of patients with neuropathy compared with the monofilament[51].

Step 5. Laboratory investigations

Several key laboratory tests can help to refine the diagnosis (Table 4).

REFERRAL TO NEUROLOGY

Patients with diabetes who require referral to a specialist include those with an acute–rapid progression or relapsing–remitting pattern of neurological symptoms and signs; predominance of motor symptoms and deficits; acute, asymmetric or proximal involvement; and the absence of other microvascular complications[52].

Table 4 | Laboratory investigations to rule out other causes of peripheral neuropathy

Laboratory tests	
Comon/simple	Serum glucose, HbA1c, oral glucose tolerance test, vitamin B_{12}
	Erythrocyte sedimentation rate serum and urine electrophoresis
	Liver and renal function tests
	Thyroid function tests
Might require referrals depending on available resources	Anti-HIV antibodies
	Tumor (paraneoplastic) markers
	Vasculitis profile (ANA, ANCA, Ro/La, cryoglobulin)

ANA, anti-nuclear antibodies; ANCA, anti-neutrophil cytoplasmic antibodies; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; PN, peripheral neuropathy.

CONCLUSION

The underdiagnosis of PN, especially in primary healthcare in SEA, creates a huge burden of hidden disease. This has a major impact on the quality of life as a result of painful neuropathic symptoms and morbidity due to foot ulceration and amputation, as well as increased mortality. An awareness and sense of urgency amongst patients and healthcare providers is required, and primary care physicians require access to simple tools to help them diagnose peripheral neuropathy.

DISCLOSURE

The authors declare no conflict of interest.

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