

Epidemiology of Peripheral Neuropathy: An Indian Perspective

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Abstract

Peripheral neuropathy (PN) is a common disorder and presents as diagnostic and therapeutic challenge to physicians and neurologists. In epidemiological studies from India from various regions the overall prevalence of PN varied from 5 to 2400 per 10,000 population in various community studies. India is composed of a multiethnic, multicultural population who are exposed to different adverse environmental factors such as arsenic and lead. Use of different chemotherapeutic agents with propensity to affect peripheral nerves, increasing methods of diagnosis of connective tissue disorders and use of immunomodulating drugs, growing aging population is expected to change the spectrum and burden of peripheral neuropathy in the community. The other important aspect of peripheral neuropathies is in terms of the geographical and occupational distribution especially of toxic neuropathies like arsenic which is common in eastern belt; lead, mercury and organo-phosphorous compounds where occupational exposures are major sources. Inflammatory neuropathies either due to vasculitis or G B Syndrome, chronic inflammatory polyradiculopathies are another major group of neuropathies which is increasing due to increase longevity of Indian subjects and immunological impairment, also adds to morbidity of the patients and are potentially treatable. Leprous neuropathy is common in India and although its frequency is significantly decreasing because of national control program yet pure neuritic form still remains a cause of concern and similar is the case with another infective cause like diphtheric neuropathy. Thus this article is an attempt to cover major categories and also highlight the areas where further studies are needed.

Keywords: Diabetic neuropathy, epidemiology, Guillain–Barre Syndrome, Hansen neuropathy, India, toxic neuropathy

INTRODUCTION

Peripheral neuropathy (PN) is a group of heterogeneous disorder with a wide etiological spectrum and presents to physicians and neurologists in the community frequently. Various epidemiological studies from India showed wide prevalence varying from 5 to 2400 per 10,000 population in different community studies [Table 1]. In a rural setting, it is less frequent and comparable with studies from eastern and southern regions. However, urban studies show higher rates. Exceptionally, high prevalence was noted among Parsis^[1] and in urban slum.^[5] The high rate in Parsis is probably related to aging population, and in urban slum, it may be due to nutritional and adverse environmental factors and needs further study.

In a hospital-based study from Eastern India^[7] out of 225 patients of acute and chronic PN, Guillain–Barre Syndrome (GBS) was the most common (24.8%), followed by diabetes (11.1%), hereditary sensory motor neuropathy (7.55%), chronic inflammatory demyelinating neuropathy (7.55%), Hansen (4.8%), alcoholic/nutritional (3.55%), and entrapment

neuropathy (3.55%). In 17.3% of patients, no etiology could be defined.

There are many papers on PN from India which are often case reports and small series, but no holistic compilation of data on epidemiology of PN was available. India is composed of a multiethnic, multicultural population who are exposed to different adverse environmental factors such as arsenic and lead. Further, use of different chemotherapeutic agents with propensity to affect peripheral nerves in different malignant diseases, increasing diagnosis of connective tissue disorders, and use of immunomodulating drugs, growing aging population is expected to change the spectrum and burden of PN in the community.

Hence, we plan to review the epidemiology of PN in the context of Indian scenario to highlight important peripheral

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Table 1: Prevalence of peripheral neuropathy in various parts of India

Region of India	Author	Year	Place	Design	Rural/urban	Population	Prevalence (/10,000)
West	Bharucha <i>et al.</i> ^[1]	1991	Mumbai	CB/CS	Urban	14,014	2400
East	Das and Sanyal ^[2]	1996	Malda, West Bengal	CB/CS	Rural	37,286	750
	Das <i>et al.</i> ^[3]	1998	Malda	CB/CS	Urban	8763	50.2
	Saha <i>et al.</i> ^[4]	2003	Baruipur, West Bengal	CB/CS	Rural	20,842	8.0
	Samsuzzaman <i>et al.</i> ^[5]	2014	Kolkata	CB/CS	Urban Slum	160	2063
Southern	Gourie-Devi <i>et al.</i> ^[6]	2004	Bangalore	CB/CS	Urban	51,502	5
					Rural	51,055	8.4

CB/CS = Community based/cross-sectional

neuropathies and also find deficiencies where further research is needed for planned epidemiological studies and possible direction to the occurrence of underlying etiology and risk factors for diagnostic and therapeutic targets.

Search strategy

We comprehensively searched the literature, using electronic medical databases (EMBASE, MEDLINE, Cochrane, PubMed Publisher, and Google Scholar), to identify published studies reporting the prevalence or incidence of polyneuropathy in the general population in India with keywords such as “PN - epidemiology” ($n = 23,020$). Furthermore, subtopics were searched with keywords such as “epidemiology of leprosy” ($n = 23,300$), “acute inflammatory demyelinating polyradiculoneuropathy (AIDP)/Landry–GBS Indian studies” ($n = 820$), and chronic inflammatory demyelinating polyneuropathy (CIDP) ($n = 2490$). Studies based on case series were included along with cross-sectional, retrospective, prospective studies, whereas case reports and Western data were found relevant. Hand search was also made from national journals such as Neurology India, Annals of Indian Academy of Neurology, and Journal of associated physician of India. Relevant articles and research papers in the past 35 years (1981–2016) were taken up.

NEUROPATHY RELATED TO DIABETES AND OTHER METABOLIC CAUSES

Diabetic neuropathy

Diabetes mellitus (DM) is a common cause of neuropathy worldwide. Prevalence of PN in diabetic patients ranges from around 10.5% to 32.2% in various studies across India [Table 2], and up to 50% patients will eventually develop neuropathy during the course of their disease according to Western literature.^[20]

Most of the studies from five regions have been provided in Table 2 on diabetic PN. There is a higher prevalence of DM in India compared with the West.^[21] However, most of the studies in India are either hospital or clinic based. Thus, the conclusions were often biased.

Above studies^[7-19] showed that age, duration of diabetes, dyslipidemia, glycosylated hemoglobin, microvascular complications, macrovascular complications, and alcoholic status are risk factors for the development of PN.

Neuropathy with impaired glucose tolerance

Many studies have noted that in idiopathic PN patients, glucose tolerance test results are abnormal. In a study of 107 patients of idiopathic neuropathy who were tested with glucose tolerance test, 13 had DM, and 36 had impaired glucose tolerance (IGT), which they note is almost 3 times the prevalence among previously published control patients.^[22] In another study from South India, IGT group exhibited a significantly lower mean nerve conduction velocity (NCV) when compared with normal participants and warrants early screening.^[23]

Uremic polyneuropathy

Chronic kidney disease (CKD) affects all levels of the nervous system. In a cross-sectional study from Andhra Pradesh,^[24] out of 74 patients of CKD, 65% of the study population was suffering from peripheral nerve dysfunction. It was more prevalent in elderly (>65 years), patients with longer duration of CKD, males, and patients with creatinine clearance <15 ml/min. CKD may also be present with entrapment neuropathies, autonomic neuropathies, and cranial neuropathies. In a study to evaluate the involvement of inner ear and eighth nerve in CKD patients, out of 46 patients with normal hearing included in the study, there was a statistically significant difference in the mean absolute latency of wave I, III, and V and mean inter-peak latency I–III, III–V, and I–V suggestive of subclinical involvement of auditory end organs and auditory nerve and it worsened with duration of disease, blood urea levels (>200 mg%), and advancement of stage of CKD.^[25]

NEUROPATHY DUE TO INFLAMMATION AND INFECTIOUS ETIOLOGY

Guillain–Barre syndrome

GBS affects between 1 and 4/100,000 of population annually throughout the world,^[26] with complications such as respiratory failure requiring ventilation in approximately 25%,^[27] persistent disability in approximately 20%,^[28] persistent fatigue in 67%,^[29] and death in 4%–15%.^[27]

After the first decade of life, there is an escalating increase of 20% with each passing decade of life. Male and female gender ratio has been observed to be 1.78:1.^[30] Nearly two-thirds of cases are preceded by symptoms of upper respiratory tract infection or diarrhea and rarely vaccination.^[31]

Table 2: Epidemiology of diabetic neuropathy

Region	Author	Year/place	Design	Rural/urban	Number of cases	Prevalence (%)	Sex	Risk factor
South India	Pradeepa <i>et al.</i> ^[8]	2008/Chennai	PB/CS	Urban	1629	26.1	Male = female	Age, HbA1c, duration
	Raman <i>et al.</i> ^[9]	2012/Chennai	PB/CS	Urban	1414	10.5	NA	Age
	Ashok <i>et al.</i> ^[10]	2002/Chennai	?Clinic based	Urban	1000	19.1	Male = female	Duration of DM, age
	D'Souza <i>et al.</i> ^[11]	2015/Mangalore	Hospital based	Urban	208	32.2	Male	Smoking, age
	Rani <i>et al.</i> ^[12]	2010/Chennai	Population based	Urban	1401	18.84	NA	Age, duration, macroalbuminuria, retinopathy
North India	Bansal <i>et al.</i> ^[13]	2014/Chandigarh	Hospital based	Urban	586	29.2	Male = female	Age, duration, dyslipidemia, HbA1c, other microvascular complication, macroalbuminuria
	Gill <i>et al.</i> ^[14]	2014/Lucknow	Hospital based/prospective	Urban	195	29.2	Male > female	Age, duration
	Agrawal <i>et al.</i> ^[15]	2014/Bikaner	Clinic based	Urban	11,157	26.8	-	Age, duration, HbA1c, hypertension
	Agrawal <i>et al.</i> ^[16]	2004/Bikaner	Clinic based	Urban	4067	30.1	NA	Age, duration, HbA1c, hypertension
North East India	Dutta <i>et al.</i> ^[17]	2005/Imphal	Hospital based	Urban	100	29.5	Female > male	Age, SBP, PPBS duration
East India	Kumar <i>et al.</i> ^[18]	2016/Bihar	Hospital/clinic based	Urban	100	24	Female > male	NA
	Ghosh <i>et al.</i> ^[7]	2006/Kolkata	Hospital based	Urban	225	11.1	NA	NA
Combined (east, west, north and south)	Sosale <i>et al.</i> ^[19]	2014/14 centers all over India	CB/CS	Urban	4600	13.15	Male > female	Age, retinopathy

PB/CS = Population based/cross-sectional, NA = Not available, HbA1c = Hemoglobin A1c, DM = Diabetes mellitus, SBP = Systolic blood pressure, PPBS = Postprandial blood sugar, CB/CS = Community based/cross-sectional

Studies have shown cross-reactivity between infectious and neural epitopes, especially for *Campylobacter jejuni* and certain forms, for example, motor axonal forms of GBS.^[28,29] Among the electrophysiological subtypes, axonal types are common in Asian countries as compared to demyelinating in Western countries.^[30,31] However, studies from India have yielded varying results showing AIDP or demyelinating type being more common [Table 3]. However, one study from Vellore in Southern India has almost comparable proportion of demyelinating and axonal variety [Table 3]. Most of the Indian studies have shown also male dominance, and median age of occurrence is about third decades. Cranial nerve involvement is common and varied from 52.7% to 72.72% of cases from two studies. Antecedent infection was documented in 54.55%–68% of cases except the study from Vellore, Southern India, showing a rate of 7% only.

Chronic dysimmune neuropathy

The chronic dysimmune neuropathies are a clinically heterogeneous group of polyneuropathies united by their presumed immune-mediated etiology. The subdivision is based on a combination of clinical, electrophysiological, pathological, and immunological features.

Chronic inflammatory demyelinating polyneuropathy

CIDP is a chronic PN with progressive phase beyond 8 weeks. The distinction between AIDP and CIDP may be artificial as the distribution of onset phases is unimodal not bimodal^[38] and intermediate or subacute forms occur.^[39] The reported prevalence of CIDP varies greatly from 1.9 to 7.7 per 100,000 along with sparse reports of incidence ranging from 0.15 to 0.48 per 100,000 per year.^[40,41]

A study from North India^[42] on 65 patients aged between 17 and 72 years, 25 patients had secondary CIDP due to DM ($n = 16$), polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes ($n = 4$), monoclonal gammopathy of undetermined significance ($n = 2$), myeloma ($n = 1$), lymphoma ($n = 1$), and malignancy ($n = 1$). Secondary CIDP patients were older (48.35 vs. 41.0 years), had less relapsing-remitting course, and more frequent dysautonomia (7 vs. 1). Demyelinating features were more marked in primary CIDP patients with a better outcome. Hence, primary or idiopathic CIDP is common and indicative of primary immunological disturbance against large diameter nerve fibers.

Table 3: Profile of Guillain-Barre Syndrome patients in India

Author	Place/region	Number of cases	Gender predominance	Age (years)	Seasonal variations	AIDP	AMAN	AMSAN	Autonomic dysfunction	Cranial nerve	Antecedent infection	Mortality
Kalita <i>et al.</i> ^[32]	Lucknow	328	Male	Mean 30, second and fourth decade	Rainy	73.8%	13.4%	4.6%	20.4%	52.7%	66.8%	n=11 (3.4%)
Chaudhuri <i>et al.</i> (2014) ^[33]	Hyderabad	37	Male	42.3±14.1	NA	56.7%	18.9%	24.3%	NA	31.5% (IVIG group) 38.8% (plasmapheresis group)	68%	n=3
Fakih <i>et al.</i> ^[34]	Guwahati	52	Male	Third decade	Summer	73.08%	15.83%	11.54%	68.18%	72.72%	54.55%	7.69%
Gupta <i>et al.</i> ^[35]	Thiruvanthapuram	142	NA	Fourth and sixth decade	Rainy	85.2%	10.2%	None	NA	64%	52.5%	0
Alexander <i>et al.</i> ^[36]	Vellor	115	Male	31.6 years	NA	38.2%	30.4%	13.6%	NA	NA	7%	NA
Vengamma <i>et al.</i> ^[37]	Tirupati	59	NA	NA	NA	76.2%	3.4%	12.4%	NA	NA	NA	NA
Ghosh <i>et al.</i> ^[38]	Kolkata	56	Male	NA	NA	NA	NA	NA	45%	NA	NA	5

AIDP = Acute inflammatory demyelinating polyneuropathy, AMAN = Acute motor axonal neuropathy, AMSAN = Acute motor and sensory axonal neuropathy, IVIG = Intravenous immunoglobulin, NA = Not available

Vasculitic neuropathies

Vasculitic neuropathy usually presents with painful mononeuropathies or asymmetric polyneuropathy of acute or subacute onset. The disorder may be classified as being systemic or nonsystemic. The systemic vasculitides are divided into primary systemic disorders, for which there is no known cause, and secondary systemic disorders, for which a virus, drug, or connective-tissue disease causes inflammation of the vessel wall.^[43]

In a study on vasculitic neuropathy,^[44] twenty patients with vasculitic neuropathy were analyzed. Sixteen of the twenty presented with classic mononeuritis multiplex but four had distal, symmetrical, sensorimotor polyneuropathy. Only 13 patients had definitive collagen vascular disease. A large proportion (7/20) had vasculitic neuropathy as the only clinical feature. A study on rheumatoid arthritis in Indian cohorts of 74 participants has shown PN in 39.19% on NCV study, and significant association has been noticed with disease duration and rheumatoid factor.^[45] In another study on sixty systemic lupus erythematosus patients, only two patients (3.3%) had PN.^[46]

Human immunodeficiency virus-associated neuropathy

PN is one of many neurological complications of human immunodeficiency virus (HIV). Clinically, there are at least six patterns of HIV-associated PN.^[47] Distal sensory PN, which is the most common out of all HIV-associated neuropathies,^[47] can exist as two major types: primary HIV-associated distal sensory polyneuropathy (HIV-DSP) and antiretroviral toxic neuropathy.^[48]

In an Indian study on 75 patients, 40% had clinical HIV-associated sensory neuropathy (HIV-SN).^[49] HIV-SN considerably affects their quality of life. Symptomatic relief therapy is usually not satisfactory.^[50] Furthermore, antiretroviral therapy is still composed of some first-line drugs that have been demonstrated to increase the risk of PN.^[51]

Although after introduction of highly active antiretroviral therapy, the incidence of HIV-associated dementia and central nervous system (CNS) opportunistic infections have fallen,^[52] but rates of HIV-associated DSP increased with reported prevalence rates exceeding 50%.^[53] HIV-SN is more common among middle-aged participants similar to other studies.^[54] According to a Western study, two-thirds of HIV-SN is subclinical,^[55] which was less common (around 16%) in Indian study.^[49]

Leprous or Hansen neuropathy

Leprosy is the most common treatable cause of neuropathy.^[56] Multidrug treatment and WHO surveillance programs are having a major impact on disease occurrence. Between 1990 and 1994, there was a 55% fall in the worldwide prevalence.^[57] Leprosy has been eliminated globally, as the number of cases has decreased from 5.4 million in 1985 to 0.24 million in 2013, and the prevalence rate has come down to 0.37 cases per 10,000.^[58] South-East Asia region currently has highest

prevalence with 72% of the global leprosy burden and India accounted for 58.85%.^[59] A total of 86,000 cases were on record as on April 1, 2014, giving a prevalence rate of 0.68 per 10,000 population.^[60] Clinical case series estimate that 4%–8% of all leprosy is limited to only peripheral nerves producing diagnostic challenge.^[61,62]

According to Indian studies, pure neuritic leprosy constitutes about 2.17%–5.3% of leprosy patients [Table 4]. At present, the endemic and hyperendemic areas of India are in the North and East. Pure neuritic leprosy is more common in men. The disease has been reported from 5 years to 69 years and it is most common in the 15–30 age group [Table 4].

The most common pattern of involvement in leprosy is mononeuritis multiplex. However, mononeuropathy, cranial neuropathies, or polyneuropathy also occur. In a study on cranial neuropathies in leprosy, greater auricular nerve conduction study (NCS) was found abnormal in 10 of the 12 patients, thus emphasizing the usefulness of the procedure in diagnosis.^[69] Deformity was observed in about one-third of cases. Associated skin lesion was documented between 21% and 49% of cases. Type 1 reaction is more common than type 2 reaction [Table 4].

Diphtheritic neuropathy

Diphtheria is caused by toxin-producing strains of *Corynebacterium diphtheriae* spread by human-to-human contact. Diphtheritic polyneuropathy (DP) is recognized as one of the most severe complications of diphtheria. Among 20,000 cases of diphtheria reported by the WHO during 2007–2011, 17,926 (89.6%) cases were from India alone.^[70] Most persons with diphtheria in India are either partially immunized or unimmunized. Profile of DP in various studies is described in Table 5. Diphtheritic neuropathy has been reported from all zones of India. It is more common among males and more common in unimmunized and partially immunized person. Even among those with background of complete immunization, 10%–45% of patients from different series have been affected. Latency of disease is variable. In unimmunized person, limb involvement is common.

TOXIN-INDUCED NEUROPATHIES

Toxins may be environmental, occupational, recreational, or iatrogenic. In India, Ayurveda, Homeopathy, and Arabic medicine are potential sources of toxicity. In a survey, 14 of the seventy herbal medical products available commercially were found to contain lead in 13 (median concentration 40 mg/g; range, 5–37,000), mercury in 6 (median concentration, 20,225 mg/g; range, 28–104,000), and arsenic in 6 (median concentration 430 mg/g; range, 37–8130).^[78] One should be cautious when evaluating a case of PN about possible toxic causes. In early stage, it is reversible, but in advanced stage, it becomes progressive and irreversible.

Arsenic

Arsenic exposure may be occupational (smelting, mining, tanning, and numerous manufacturing processes),^[79]

Table 4: Epidemiology of neuropathy in leprosy

Author	Place	Number of cases	Study period	Study type	Age (years)	Sex predominance	Pure neuritic	Deformity	Skin lesion	Reaction
Mahajan et al. ^[62]	Maharashtra, Pune	3853	NA	Clinic based	NA	NA	179 (4.6%)	87 (48.6%)	0%	NA
Narang et al. ^[63]	Chandigarh	906	2006-2013	Retrospective	36.9±16.2	Males (85.4%)	5.3%	66.7%	NA	16.6% Type I
van Brakel et al. ^[64]	North India	303	2 years/ prospective	Prospective multi centre	32.8	Males (72%)	4.3%	-	21%	19.8% Type I, 2% Type II
Kumar et al. ^[65]	Chandigarh	1542	1993-2003	Hospital based	15-35 (60%)	Males	4.2%	30.8%	0%	NA
Bhat and Chaitra ^[66]	South India/ Mangalore	55	2011-2012	Retrospective	36-50 (41%)	Males	2.17%	34.78%	23%	34.78% Type I, 8.2% Type II
Sarkar et al. ^[67]	West Bengal	244	2006-2007	Hospital based	NA	Males	9.4%	20.1%	NA	NA
Mendiratta et al. ^[68]	New Delhi	686	2000-2004	Retrospective	15-30	Males	4.6%	50%	NA	NA

NA = Not available

Table 5: Profile of diphtheritic polyneuropathy in various studies in India

Attributes	AFP surveillance ^[71]	Delhi (2008-2010) ^[72]	Gujarat (2011) ^[73]	Andhra Pradesh (2015) ^[74]	Assam (2003) ^[75]	Uttarakhand (2005-2010) ^[76]	South India (1992) ^[77]
Sample size	15	48	60	13	101	61	228
Age group	<15 years	4.25 years	10-19 (46.7%) 1-4 (11.7%)	5-13 years	82% <15 years	5.16±2.9 years	5-15 years
Gender predilection	NA	Male	Male	NA	Male	Male	Male
IS-complete	NA	NA	45%	NA	10%	NA	NA
IS partial	NA	NA	NA	47%	20%	4.1%	NA
Unimmunized	NA	100%	NA	53%	70%	96%	NA
Latency in days	10	10	NA	15%-30%	NA	21	NA
Palatal palsy	15%	6%	NA	60%	NA	18.8%	5.7%
Limb involvement	85%	94%	NA	40%	NA	NA	NA
CSF	100% normal	NA	NA	80% protein elevation	NA	NA	NA
Mechanical ventilation	20%	60%	NA	none	NA	16.3%	NA
Recovery	NA	NA	NA	21-102 days	75%	NA	NA
Fatal outcome	46%	NA	NA	8%	16%	35.48%	13.21%

IS = Immunization status, CSF = Cerebrospinal fluid, AFP = Acute flaccid paralysis, NA = Not available

environmental (groundwater contamination, combustion fumes of contaminated fossil fuels and arsenate-treated wood, and contact with arsenic-containing pesticides and herbicides),^[80] and iatrogenic medicinal exposure including folk and herbal medicines.^[78] Arsenic is also a homicidal or suicidal agent.^[80,81]

In some parts of the world like Bangladesh (79.9 million), India, including the state of West Bengal (42.7 million), subacute onset or chronic arsenic neuropathy commonly reflects exposure to drinking water contamination from geologic, mining, or other industrial sources or ingestion of arsenic-containing homeopathic medicines.^[80,82,83] Chronic arsenic intoxication occurs either adulteration of opium or country liquor (common in North India) and contaminated ground water (Common in West Bengal and Bangladesh). Occurrence of PN has been observed in 11%–41% of cases, common in subacute exposure (87%) than chronic (37.3%).^[80,83]

Acute arsenic neuropathy usually follows a single massive exposure, after which neuropathy appears within 5–10 days. Initial symptoms include paresthesias and burning pain, distal numbness and tingling, muscle aches, and distal weakness. The neuropathy progresses over weeks despite no additional exposure (coasting).^[84]

Some cases, the neuropathy results in flaccid paralysis resembling GBS.^[85]

Lead poisoning

Lead is a nonferrous toxic metal that is absorbed across respiratory and gastrointestinal membranes.^[86] Exposure may result from consumption of illicit whiskey made in lead-lined stills,^[87] lead-containing candy, powdered food coloring, herbal medications, food contaminated by glaze pigments in ceramic dishes,^[88] and occupational (smelting reprocessing

of lead-containing products, demolition of lead-painted structures, manufacturing paint pigments, and repair of automobile radiators).^[89]

In a survey on fifty petrol pump workers and garage attendants in Orissa, blood lead levels ranged between 20 and 80 ng/dl and complained of fatigue (50%), abdominal pain (20%), sleep disturbance (20%), and tremors (14%). NCS revealed subclinical motor neuropathy in four participants.^[90] Radial neuropathy in five patients aged 30–37 years was reported in battery factory or battery shop workers (wrist drop in four and finger drop in one). All patients had elevated blood lead level (37.8–107.8 mg/dL)^[91] with subtle changes in the form of reduced compound motor action potential (CMAP) on NCS.^[91]

Elemental mercury

Mercury is used in the chlor-alkali industry, metal plating, tanning processes, thermometers, electromechanical switches, a component of dental amalgams, and antiseptic and purgative medication.^[92]

Acute exposure to high-level mercury vapor produces erosive bronchitis, interstitial pneumonitis with pulmonary edema, and renal insufficiency.^[93] Signs of chronic intoxication include behavioral changes, postural tremor, and neuropathy.^[94,95]

Chronic exposure is characterized by insidious onset of stocking-distribution sensory loss, Romberg sign, absent ankle reflexes, and postural tremor with mild motor involvement^[93] and generally resolve after removal from exposure although there may be a residual tremor.^[96]

Evidence of mild neuropathy has been identified among chlor-alkali workers exposed to elemental mercury with 28% of workers showing clinical evidence of neuropathy having

markedly elevated urinary mercury excretion levels above 850 µg/L.^[93,96]

In one study, one-fifth of both US-manufactured and Indian-manufactured Ayurvedic medicines purchased through the internet contain detectable lead, mercury, or arsenic.^[97]

Kodaikanal, India, suffered mercury contamination due to emissions and waste from a thermometer factory. Results from a study on mercury in Kodai Lake waters showed that pollution of the lake has taken place due to mercury emissions by the factory.^[98]

Organophosphorus poisoning

Acute organophosphate (OP) poisoning is a significant cause of morbidity and mortality in developing countries including India. Although no exact estimates are available, hospital-based studies suggest that it is the most common poisoning in India with nearly half of the admissions to the “emergency” with poisoning being due to these compounds.^[99-102]

According to the WHO, one million serious accidental and two million suicidal poisonings due to insecticides occur worldwide every year, of which 200,000 die and most of these deaths occur in developing countries.^[103]

In a report on 200 cases of OP poisoning for suicidal ingestion, the clinical manifestations included miosis in all, impaired consciousness (10%), fasciculations (27%), convulsions (11%), delirium (50%), and paralysis (26%). The paralytic signs were divided into type I and type II (intermediate syndrome). Type I paralysis manifested with impaired consciousness and bipyramidal signs due to excessive cholinergic stimulation of muscarinic receptors and responded to atropine. Type II paralysis manifested from 24 to 96 h with wasting and weakness of proximal muscle, areflexia, and cranial nerve palsy not responding to atropine and usually lasts for 5–6 days.^[104] Type III symptoms or delayed neurotoxicity of OPs occur after 8–12 days with severe distal weakness due to axonal neuropathy.

Electrophysiological studies by Indian investigators during such paralysis showed normal distal latency and NCV even in severely paralyzed patients with reduced CMAP amplitude more severely affected cases. Low rate repetitive nerve stimulation (RNS) did not reveal any decrement, but significant decrement was observed at high rate (30 Hz) RNS even in the absence of paralysis.^[105]

Delayed OP neurotoxicity, especially in relation to triorthocresyl phosphate (TOCP), has been reported following outbreaks in Mumbai, in which 58 patients were affected.^[106] Four outbreaks have been reported from Bengal due to imported flour contaminated with TOCP^[107] and adulteration of rapeseed oil.^[108] In a report on 592 patients, 50% patients had diarrhea and vomiting initially. After an interval of 1–3 weeks, paralytic phase developed ranging from quadriplegia to foot drop and wrist drop. Proximal lower limb muscles were affected in 40% patients, rare upper limb involvement and ankle reflexes were absent in all with evidence of axonal degeneration and reinnervation on

electrodiagnostic study. Later, myelopathic features appeared in up to 65% cases. After 2 years, 25% patients recovered completely and about 65% patients returned to occupation.^[109]

Alcoholic neuropathy

Polyneuropathy has been reported to be present in 13%–66% of chronic alcoholics.^[110] The relative risk of polyneuropathy in chronic alcoholics is estimated at 3.9 times.^[111] The pathophysiology of alcoholic polyneuropathy combines the toxic effect of alcohol with nutritional deficiency.^[112] Both alcoholic neuropathy and thiamine-deficiency neuropathy are mainly of axonal type and are usually characterized by painful sensory disturbance and weakness in the distal lower extremities. Autonomic dysfunction often occurs. Pure alcoholic neuropathy without accompanying thiamine deficiency mainly affects small fibers, whereas thiamine-deficiency neuropathy predominantly affects large fibers polyneuropathy with predominantly motor symptoms.^[112]

In a study on 33 patients with liver cirrhosis, sensory motor axonal neuropathy was present in 7 (21%) and nerve conductions were abnormal in 24 (73%) which was present in both alcohol and nonalcohol-related cirrhosis. Neuropathy was subclinical in majority of patients with cirrhosis (73%) and was not related to alcohol.^[113]

In another study by Bajaj *et al.*,^[114] 16 out of twenty patients with cirrhosis of liver had autonomic neuropathy, and the frequency was comparable between alcoholic and nonalcoholics. The severity of autonomic neuropathy increased with severity of liver damage suggesting liver damage was primarily responsible for autonomic neuropathy.

In a study carried out on thirty patients admitted at a tertiary hospital in Southern India with a history suggestive of alcohol dependence syndrome, the prevalence of neuropathy was 63.3%.^[115]

Drug-induced toxic neuropathies

There are many drugs that cause polyneuropathy as an adverse effect. An Indian study estimated the incidence of polyneuropathy from medications or toxins to be 2%–4%.^[116] However, there are no epidemiological data but mostly anecdotal reports.

NUTRITIONAL NEUROPATHY

Malnutrition affects both peripheral and CNS. PN may coexist with myelopathy (myeloneuropathy) can be seen with nutritional neuropathies.

They most commonly affect neuron itself and myelin sheath in peripheral nervous system resulting in either clinical or subclinical neuropathy. In a study on 67 children, nerve conduction velocities were found to be markedly decreased in protein energy malnutrition (PEM) Grades 3 and 4 as compared to the controls. Nerve conduction velocities were lower in children when the age of onset of malnutrition was <12 months.^[117] In another study on 43 children, abnormality

of motor nerve conduction was directly related to the severity of PCM and presence of hypotonia and/or hyporeflexia. Nerve dysfunction was not only entirely due to PEM but also contributed by many nutrient deficiencies.^[118] Large myelinated fibers and sensory fibers are more affected than small myelinated and motor fibers.^[119]

Vitamin B₁₂, B₆, niacin, and thiamine deficiencies result in PN of predominantly axonal distal symmetrical sensory-motor type. However, well-designed studies on these are lacking.

Tropical ataxic neuropathy

Tropical myeloneuropathies are classified into two clinical syndromes that can have overlapping features – tropical ataxic neuropathy (TAN) and tropical spastic paraparesis TAN are predominantly a SN seen in malnourished populations who consume large quantities of cassava. In a study of clinical and laboratory profile of forty TAN cases diagnosed in a tertiary referral center in Kerala, demographic characteristics included female preponderance, peak age at onset in the thirties, rural residence, and poor socioeconomic status. In addition to SN, 90% had decreased hearing, 50% decreased vision, and 25% had spasticity of lower extremities. Serum, urine, and sural nerve thiocyanate levels were significantly elevated in the patients and cessation of cassava intake, and better nutrition caused improvement in the neurological disability.^[120]

CRITICAL ILLNESS POLYNEUROPATHY

Critical illness polyneuropathy is a condition occurring in critically ill patients who have been on mechanical ventilation for more than 1 week and usually identified by failure to wean the patient from ventilator. Based on clinical evaluation alone, an incidence of 25%–36% has been shown in prospective studies.^[121,122] Electrophysiologic testing revealed that neuropathy and/or myopathy is present in 52%–57% of patients in Intensive Care Unit for 7 days or more.^[123] In a cohort of 100 patients with sepsis, 37 patients had features of neuropathy, 81% of which developed it in the first 14 days, Acute Physiology and Chronic Health Evaluation II score ≥ 15 , and use of neuromuscular blocking agents were significant risk factors.^[124] In another study^[125] to characterize the prevalence, time of onset, and cause of neuromuscular dysfunction in patients with severe sepsis, abnormal NCS was present in 31 out of 48 patients (63%). Development of acquired neuromuscular dysfunction could be predicted by NCS done on day 7. Presence of abnormal baseline NCS was predictive of hospital mortality (55% vs. 0% for patients with normal baseline NCS; $P < 0.001$).

PARANEOPLASTIC NEUROPATHY

In up to 50% of patients with carcinoma, PN can be due to treatment toxicity, tumorous infiltration, metabolic disturbances, or terminal cachexia.^[126] Neuropathy is defined as paraneoplastic when none of the above causes are detected or

when cancer-related immunological mechanisms are involved. About 15% of patients with cancer develop a paraneoplastic sensorimotor neuropathy, which is usually mild and develops during the terminal stage of the disease.^[127] There is another group that may precede the diagnosis of the tumor. The majority of paraneoplastic neuropathies develop rapidly in a matter of weeks and subsequently stabilizes or continues to progress until the patient's death.^[128] In patient in remission, development of paraneoplastic neuropathy may signify tumor recurrence.^[129]

In a study on paraneoplastic vasculitic neuropathy (PVN), out of 14 cases of paraneoplastic neuropathies, four had PVN with age of onset more than 50 years. Pain was seen in three patients. Two patients were previously treated for a thymoma and two were diagnosed with a colonic carcinoma and lung carcinoma, respectively.^[130]

HEREDITARY NEUROPATHIES

The inherited neuropathies can broadly be classified into two groups: Those in which neuropathy is primary (e.g. Charcot–Marie–Tooth disease, CMT) and those in which neuropathy is part of generalized neurological or multisystem disorder.

CMT is a common form of inherited PN and estimated prevalence is 40–82 per 100,000 people.^[131,132] In Indian hospital-based study, the frequency was found to be 4.8%.^[7]

In a series of twenty patients of CMT type 1, the inheritance pattern was autosomal recessive (AR) in four families and five sporadic cases were present.^[133] Males were commonly affected, and predominant pattern was axonal type.

Amyloid neuropathy is another hereditary neuropathy due to deposition of transthyretin or less commonly other proteins, in peripheral nerves. It may be an acquired disorder secondary to B-cell dyscrasia and immunoglobulin light chain deposition. In a report from North-West India, six members of a family spanning two generations were affected with polyneuropathy, autonomic neuropathy, vitreous, and cardiac involvement.^[134]

In hereditary neuropathy associated with systemic degeneration, most cases in India have been described in association with patients of spinocerebellar ataxia by Wadia *et al.*^[135] having sensory axonal neuropathy and AR hereditary SN with spastic paraplegia described by Thomas *et al.*^[136] in five patients, four of whom were from India.

Limitation

Although it has been an effort to put into perspective the major studies in India on PN and its subtypes, there remains many untouched portions such as entrapment neuropathies, cranial neuropathies, porphyria-associated neuropathies due to drugs and toxins apart from the mentioned, plant and animal toxins-induced neuropathies, and traumatic neuropathies.

CONCLUSION

Thus, PN is a group of neurological disorder with varied etiologies caused by hereditary, metabolic, toxic, and environmental causes. In India, because of varied ethnicity and environmental causes, PN due to diabetes, GBS, leprosy, toxin-like arsenic, and TOCP poisoning are common. Yet, there are other such as vasculitic neuropathies, drug-induced neuropathies, and hereditary neuropathies where well-designed studies are lacking. However, many of our series are hospital based or clinic based which had got inherent bias, we need more community-based studies to search for the real scenario in different parts of India. The studies also highlight the regional differences which are important to know to arrive at appropriate pattern of PN and undertaking proper preventive measures. Yet, many a times, even after intensive investigation, one may not arrive at an etiological diagnosis warranting long-term follow-up.

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