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ORIGINAL ARTICLE

Mortality in Asian Indians with Charcot's neuroarthropathy: a nested cohort prospective study

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Abstract

Aims We studied mortality in individuals of diabetes with or without Charcot neuroarthropathy (CN).

Methods People attending diabetic foot care facility with CN of foot (Cohort 1) were prospectively evaluated. Details pertaining to the duration of diabetes, microvascular and macrovascular complications, foot ulcer, amputation and mortality outcomes were recorded and compared with those without foot complications (Cohort 2) by multivariate logistic regression.

Results Data for 260 individuals of diabetes with CN and 520 individuals without CN were analysed. Mean age at presentation with CN was 55.8 ± 9.1 years, and duration of diabetes was 12.9 ± 7.8 years. 39.8% individuals with CN had foot ulcer, and 15.3% had amputation. People with CN were younger (55 ± 9.1 vs. 59.9 ± 8.1 years, $p < 0.001$) and had higher prevalence of microvascular complications. A total of 39 (15%) individuals with CN and 50 (9.8%) ($p = 0.03$) individuals without CN died during median follow-up of 40(24–51) months. People with CN had 2.7 times (OR 2.72, 95% CI 1.4–5.2, $p = 0.003$) increased mortality risk when matched for potential confounders. Prevalent CAD and low eGFR predicted higher mortality in people with CN.

Conclusions People with Charcot neuroarthropathy have almost three times increased risk of mortality despite being younger at presentation.

Keywords Charcot neuroarthropathy · Asian Indians · Mortality · Amputation · Diabetic neuropathy

Introduction

Diabetes as a non-communicable disease is a major health challenge worldwide. With nearly 72.9 million people with diabetes, India has the second largest population of individuals with diabetes in the world [1]. The increasing number of individuals with diabetes translates to an increased burden of comorbidities that include microvascular and macrovascular complications. Charcot neuroarthropathy (CN) is an underrecognised consequence of diabetic neuropathy. The diagnosis of CN is often overlooked, especially in early stages due to less awareness amongst clinicians [2]. Hence, CN may result in fracture, fixed deformities, ulceration, osteomyelitis and limb loss [3].

It is known that the people with diabetic neuropathy and foot ulcer have higher mortality compared to those without neuropathy or ulcer [4]. But the data regarding mortality in CN are still sparse and non-conclusive. Two prior studies by Armstrong et al. [5] and Fabrin et al. [6] have shown lower mortality in contrast to Gazis et al. [7] who have reported higher mortality risk (44.7%) in acute CN compared to healthy controls. A higher mortality was also observed in both acute CN and uncomplicated neuropathic foot ulcer patients in another study, without survival difference between two groups [8]. Hence, it was concluded by authors that underlying neuropathy, rather than CN, is independently associated with increased mortality in diabetes.

However, Sohn et al. [9] in a large retrospective cohort study showed that CN is associated with a significantly

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increased mortality risk that is independent of incident foot ulcer or other diabetic comorbidities including neuropathy. Thewjitcharoen et al. [10] in a study of 40 patients with CN showed that 8% of acute CN and 15% of chronic CN patients die during a median follow-up of 57 months. Overall, most of the prior studies with CN were retrospective in nature, lacked control group and were based on small cohort that precludes strong conclusions. Moreover, the epidemiology of Charcot neuroarthropathy may vary with geographic regions because of late detection of Charcot foot and lack of specialised centres in developing world; hence, it becomes pertinent to assess mortality risk in our population with CN. Therefore, we planned to study mortality outcome amongst individuals of diabetes with CN in comparison with those without CN.

Patients and methods

The details of all individuals attending the tertiary care foot clinic in North India with diabetes and foot complications were captured in a pre-designed case record form and entered into an electronic database. Amongst this cohort, individuals with diabetes and CN (Cohort 1) were prospectively followed from January 2013 to June 2018. An informed written consent was obtained from all participants, and study protocol was approved by the Institute Ethics Committee. Information recorded pertained to age, gender, height, weight, body mass index (BMI), duration of diabetes and type of diabetes. Details of a thorough neurological examination including vibration perception threshold (VPT), hot, cold and 5-g monofilament perception at 5 standardised plantar sites on either foot were noted. Diabetic peripheral neuropathy was considered as "present", if VPT was > 25 mV and/or absence of monofilament perception in the presence or absence of symptoms suggestive of neuropathy. The participants details of other microvascular complications and macrovascular complications of diabetes including nephropathy (based on eGFR calculated from creatinine clearance by CKD-EPI < 60 ml/min/1.73 m^2 and/or presence of micro- or macroalbuminuria), retinopathy on fundus examination, coronary artery disease (CAD) (history of coronary intervention/revascularisation, pathological findings on coronary angiography, or prior records documenting CAD), peripheral vascular disease (PVD) (defined as non-palpable pedal pulses and/or ABI < 0.9 or prior history of revascularization of limb arteries), cerebrovascular accident (CVA) (history of CVA with or without hemiplegia, hemiparesis and dysarthria or prior records documenting CVA), presence of pedal ulcer or development of new ulcer during follow-up, previous amputation or new amputation during follow-up were recorded. Minor amputation was defined as digit amputation or that allowed plantigrade walking after amputation and major amputation was defined as below knee or more proximal amputations.

Acute Charcot foot was defined by the clinical presentation with warm, swollen foot with or without erythema of the underlying skin and temperature difference of > 2 °C at the involved site compared to a similar site on the opposite foot after exclusion of other conditions resembling Charcot foot including cellulitis, deep vein thrombosis, gout, septic arthritis, etc. Chronic CN was considered, if patient had fracture or dislocation with or without gross deformity of foot, with the presence of sensory neuropathy and/or prior history suggestive of acute CN. Individuals fulfilling criteria for acute CN in the setting of chronic CN were considered as "acute on chronic" CN. Site of foot involvement, i.e., forefoot, midfoot or hindfoot and dexterity whether right, left or both feet was also documented. In case of doubtful clinical diagnosis of CN, magnetic resonance imaging (MRI) of foot or nuclear imaging (Triple phase ^{99m}Tc scintigraphy) was performed, if MRI was contraindicated. Patients with foot ulcer, the diagnosis of osteomyelitis was considered after clinical evaluation, positive probe to bone test (palpable bone on inserting a blunt metal probe and/or radiological imaging), MRI or F18-FDG labelled leucocyte PET/CT [11].

Assessment of mortality

Individuals were recalled 3–4 monthly for glycemic evaluation, or earlier in case of occurrence of acute events including new-onset diminished vision, uraemic symptoms, CAD, PVD or ulcer and were entered into dataset, subsequently. Patients were contacted telephonically if they missed 2 successive follow-up visits, and reason for missing the follow-up visits was recorded. If the reason for lack of follow-up was the death of patient, date and cause of death was inquired and entered into dataset. The reasons for mortality were ascertained from hospital and patient records and were labelled as unspecified in the absence of such details.

Details of individuals with diabetes without CN or any foot complications pertaining to demographics and complications of diabetes were recorded in another cohort (Cohort 2). The cohort was matched for the duration of diabetes with Cohort 1 (1:2 matching). Individuals in both the cohorts were followed, and time to event was calculated from the date of study entry till the date of death or 30th June, 2018, whichever occurred earlier.

Statistical analysis

Baseline variables are presented as mean ± SD (if normally distributed) and median (IQR), in case of skewed distribution. Normality of data was assessed with Smirnov–Kolmogorov test. The categorical variables are presented as

percentage. Missing data were dealt by excluding patients from particular analysis if the record did not contain data for required variables. For categorical variables, differences were analysed by means of Chi-square test. Differences in continuous variables were analysed by means of two-tailed Mann–Whitney *U* test. Multivariate logistic regression was used to determine statistical predictors of mortality. The model was obtained using mortality as the "dependent variable" and age, gender, duration of diabetes and presence of prior or new-onset retinopathy, nephropathy, PVD, CAD, CVA, prevalent ulcer and amputation as independent covariates. Adjusted and unadjusted odds ratio was calculated using logistic regression. P value less than 0.05 was considered to be statistically significant.

Results

A total of 260 individuals of diabetes presented with CN out of 1156 individuals (22.5%) with foot complications. Sixty-three out of 260 individuals (24.2%) presented with acute CN, 49 patients with acute on chronic CN (18.8%) and 148 with chronic CN (56.9%). Mean age at presentation with CN was 55.8 ± 9.1 years, and duration of diabetes was 12.9 ± 7.8 years. Almost two-thirds were (69.6%) men and majority (99%) were having type 2 diabetes. Baseline characteristics of Cohort 1 (sub-categorised on the basis of presentation) are shown in Table 1.

A prior or incident foot ulcer was observed in 39.8% of individuals and 15.3% underwent subsequent amputations (minor or major). Foot ulcer and amputation were more prevalent in chronic CN. Right foot was more commonly involved (44.6%), and both feet were involved in 14.6% of patients. Midfoot was the most common involved site (62.3%) followed by forefoot (22.6%) and hindfoot (12.3%). Neuropathy (80%) was the most prevalent microvascular complication followed by retinopathy (63.8%) and nephropathy (49.2%) in Cohort 1. Amongst macrovascular complications, PVD was observed in 21.5%, CAD in 8.5% and CVA in 4.2% respectively. 68.1% of individuals had hypertension in Cohort 1.

The comparative baseline characteristics of individuals of diabetes without CN (Cohort 2) and with CN (Cohort 1) are shown in Table 2. All the microvascular complications were more prevalent in Cohort 1 as compared to Cohort 2, even with similar duration of diabetes. However, CAD was more prevalent in Cohort 2 versus Cohort 1 (14.9% vs. 8.9%, p = 0.02).

Table 2 Baseline characteristics of individuals with (Cohort 1) and without (Cohort 2) Charcot neuroarthropathy

Parameters	Cohort 1 $n=260$	Cohort 2 $n=520$	p value
Age (years)	55 ± 9.07	59.9 ± 8.09	0.00
Men (%)	181 (69.6%)	450 (86.5%)	0.00
Duration of diabetes (years)	12.9 ± 7.8	12.5 ± 6.1	0.49
Retinopathy, *n* (%)	166 (64.1%)	80 (15.8%)	0.00
Nephropathy, *n* (%)	128 (50.2%)	103 (21.1%)	0.00
Neuropathy, *n* (%)	208 (80%)	93 (17.9%)	0.00
Coronary artery disease, *n* (%)	22 (8.9%)	77 (14.9%)	0.02
Hypertension, *n* (%)	177 (72.8%)	373 (72.3%)	0.87

$p < 0.05$ was considered significant

Table 1 Baseline characteristics of individuals with diabetes and Charcot neuroarthropathy

	Total $n=260$	Acute Charcot $n=63$	Acute on chronic Charcot $n=49$	Chronic Charcot $n=148$	p value
Age (years)	55.83 ± 9.07	55.01 ± 9.2	56.02 ± 7.5	56.18 ± 9.5	0.60
Men (%)	181 (69.6%)	45 (71.4%)	34 (69.4%)	102 (68.9%)	0.93
Duration of diabetes (years)	12.9 ± 7.8	12.8 ± 6.9	14.1 ± 7.9	12.6 ± 8.1	0.35
eGFR (ml/min/1.73 m^2)	65.34 ± 33.9	69.7 ± 33.5	67.7 ± 31.5	62.4 ± 34.7	0.31
Prevalent ulcer, *n* (%)	103 (39.6%)	17 (27%)	19 (38.8%)	67 (45.3%)	0.04
Foot amputation, *n* (%)	40 (15.4%)	6 (9.5%)	4 (8.2%)	30 (20.3%)	0.04
Retinopathy, *n* (%)	166 (63.8%)	35 (55.6%)	31 (63.3%)	100 (67.6%)	0.40
Nephropathy, *n* (%)	128 (49.2%)	32 (50.8%)	29 (59.2%)	67 (45.3%)	0.19
Peripheral vascular disease, *n* (%)	56 (21.8%)	11 (17.5%)	13 (26.5%)	32 (22.1%)	0.36
Coronary artery disease, *n* (%)	22 (8.5%)	5 (7.9%)	3 (6.1%)	5 (3.4%)	0.65
Cerebral vascular accident, *n* (%)	11 (4.2%)	3 (4.8%)	3 (6.1%)	5 (3.4%)	0.65
Hypertension, *n* (%)	177 (68.6%)	44 (69.8%)	31 (64.6%)	102 (69.4%)	0.58

eGFR estimated glomerular filtration rate

$p < 0.05$ was considered significant

Mortality outcomes

Thirty nine out of 260 (15.0%) patients of Cohort 1 and fifty out of 520 (9.8%) ($p=0.03$) individuals from Cohort 2 died during median follow-up of 40(24–51) months. Amongst Cohort 1, the mortality rate were numerically higher in chronic CN (56.4%) as compared to acute CN (23.1%) or acute on chronic CN (20.5%) ($p=0.9$). A subgroup analysis of Cohort 1 based on the presence of prior ulcer or amputation divulged that there were nineteen deaths in 144 individuals of CN (13.2%) without ulcer and amputation as compared to twenty deaths (17.2%) in those with CN and coexisting ulcer or amputation (OR − 1.37 {95% CI − 0.69 to 2.7}, $p=0.36$). Cardiovascular events (CVE) (30%) were the most common cause of death followed by renal failure (25.6%), infections (10.2%) and hypoglycaemia (7.7%) and unspecified in 23.1% of patients in Cohort 1. Prevalent CAD ($p=0.01$) and lower eGFR ($p=0.01$) were more common in those who died compared to survivors with CN as shown in Table 3. Mean survival in Cohort 1 after an incident diagnosis of CN was 4.49 years compared to 4.78 years ($p<0.01$) in individuals of diabetes without CN. Odds for mortality was 1.62 fold higher (OR 1.62, 95% CI 1.03–2.5; $p=0.03$) in individuals with CN as compared to those without CN. The odds for mortality were 2.72-fold (OR 2.72; 95% CI 1.4–5.2; $p=0.003$) in individuals with CN after adjusting for baseline parameters. Amongst the individuals who died during follow-up in the two groups, peripheral neuropathy was more prevalent in patients with CN (74.4% vs. 43.5%, $p=0.028$), despite being younger (56.9 years vs. 62.9 years, $p=0.003$) compared to individuals without CN (Table 4).

Table 3 Baseline characteristics of individuals with Charcot neuroarthropathy (survivors vs. non-survivors)

Parameters	Survivors $n=221$	Non-Survivors $n=39$	p value
Retinopathy, n (%)	138 (63.09%)	27 (69.2%)	0.70
Nephropathy, n (%)	108 (54.37%)	20 (52.6%)	0.36
Neuropathy, n (%)	180 (81.08%)	30 (76.92%)	0.14
Peripheral vascular disease, n (%)	44 (20.27%)	12 (30.8%)	0.34
Coronary artery disease, n (%)	14 (6.79%)	8 (20.5%)	0.01
Cerebrovascular accident, n (%)	7 (3.38%)	4 (10.3%)	0.17
Hypertension, n (%)	144 (70.93%)	32 (82.1%)	0.36
eGFR (ml/min/1.73 m^2)	67.6 ± 34.53	51.4 ± 26.5	0.01
Prevalent ulcer, n (%)	88 (39.8%)	13 (38.5%)	0.87
Amputation, n (%)	31 (14%)	9 (23.1%)	0.14

eGFR estimated glomerular filtration rate

$p<0.05$ was considered significant

Table 4 Characteristics of individuals with CN (Cohort 1) and without (Cohort 2) Charcot neuroarthropathy who died during follow-up

Parameters	Cohort 1 $n=39$	Cohort 2 $n=50$	p value
Age (years)	56.89 ± 9.92	62.9 ± 7.7	0.00
Duration of diabetes (years)	12.49 ± 7.02	13.4 ± 6.8	0.56
Retinopathy, n (%)	27 (69.2%)	9 (18.4%)	0.00
Nephropathy, n (%)	20 (51.3%)	10 (25.6%)	0.04
Neuropathy, n (%)	29 (74.4%)	10 (43.5%)	0.03
Coronary artery disease	8 (20.5%)	10 (20.4%)	1.0

$p<0.05$ was considered significant

Discussion

This is a retrospective analysis of individuals with and without CN, prospectively followed up for mortality outcomes. We observed that Charcot neuroarthropathy is associated with a higher mortality than a comparable cohort of individuals with diabetes without CN. Individuals with CN were younger at presentation in our cohort similar to that observed by Anichini et al. [12] in a population based study from Italy. Despite being younger, individuals with CN have a higher prevalence of microvascular complications compared to those with diabetes without CN. We observed that two-third of CN patients are male indicating a male preponderance for CN, as also previously highlighted by Seghieri et al. [13].

The mortality rate observed in our cohort of CN participants was less (15%) as compared to that observed by Gazis et al. (44.7%) [7], Sohn et al. (28.3%) [9] and Bergis et al. (33.3%) [14]. However, our results were comparable to Baal et al. [8] (18.6%) and Thewjitcharoen et al. [10] (12.8%). The dissimilarity in mortality amongst various studies could be attributed to differences in the baseline characteristics of the population including the age at presentation. The cohort in studies by Sohn et al. [15] and Bergis et al. [14] had a higher mean age of 63 and 69.8 years, respectively, as compared to mean age of 55.8 years in our study. Our cohort being younger had expectedly lesser mortality, since advanced age is itself a predictor of mortality.

We observed a 1.62-fold higher mortality risk in patients with CN compared to individuals of diabetes without CN. An even higher mortality risk (2.72-fold higher mortality risk) was observed in patients with CN after adjusting for various confounding variables including age, duration of diabetes, prevalent nephropathy, hypertension and CAD. The excess mortality rate with CN observed in our study is similar to that reported amongst patients with diabetic foot ulcer in Nord-Trondelag Health Study [16]. Cardiovascular events (30%) were the most common cause of death in our cohort with CN despite having a lower prevalence of

CAD at diagnosis of CN in comparison with patients without CN. This is in concordance with Bergis et al. [14] who also reported CVE (29.7%) as most common cause of death. The presence of CAD and eGFR < 60 ml/min/1.73 m^2 was found to be associated with significantly higher mortality in patients with CN even after adjusting for other baseline variables. Previous studies with CN patients have also reported CAD (Bergis et al. [14]) and presence of nephropathy (Säemann et al. [17]) as the predictors of mortality.

The pathophysiology of increased mortality risk in CN is largely unknown. Since significantly higher proportion of individuals with CN had neuropathy, retinopathy or nephropathy than individuals without CN in our study, greater burden of microvascular complications in patients of CN may have contributed to an increased mortality. In fact, it has been observed by Brownrigg et al. [18] that cardiovascular risk increases with increasing numbers of microvascular complications and simultaneous presence of retinopathy, nephropathy and neuropathy is associated with twice the risk (HR − 1.99 [95% CI 1.70–2.34]) for cardiovascular events compared to those without such complications. In the present study, the prevalence of CAD in individuals of CN was less common than those without CN, but CVE as the cause of death was similar between those with or without CN, suggesting that CN itself may predispose to CVE. An increased prevalence of CVE in individuals of CN who died may be associated with cardiac autonomic neuropathy as peripheral neuropathy and possibly autonomic neuropathy is sine qua non for CN [5].

The presence of an ulcer or subsequent amputation may be implicated in increased mortality as has been previously observed by Sohn et al. [9]. In the present study, foot ulceration was present in more than one-third of patients with CN. Foot ulcers were more commonly observed in individuals of chronic CN (45%) compared to individuals with acute on chronic CN (38.8%) or acute CN (27%). A similar prevalence of ulcer (35%) was noticed in patients with acute CN at presentation in CDUK study [19]. We did not find a significantly higher prevalence of ulcer or amputation in non-survivors, similar to the observations by Baal JV et al. [8], and mortality rates in our CN cohort were independent of the prior ulcer or amputation.

An early diagnosis and adequate treatment of CN is essential to prevent morbidity arising from subsequent foot deformity, ulcer or amputation [20]. However, as CN is associated with higher burden of microvascular complications as compared to those without CN, a timely management of coexisting comorbidities may have impact on mortality. Although many adjunctive therapies have been studied for improving outcome and quality of life in diabetic foot ulcer including negative pressure wound therapy [21] and hyperbaric oxygen therapy [22], not many therapies are available for CN. The gold standard for acute CN is total contact cast, while treatment options for chronic Charcot are still unexplored [20]. Recently, teriparatide has been investigated for prevention of progression of deformities in patients with chronic CN that may subsequently decrease amputation and morbidity, but needs long-term studies for further substantiation [23].

The strength of the study includes large dataset of CN patients and rigorous prospective follow-up. The accuracy of data collection was reasonably good, but some variables were missing for few patients. Since our study is based on a single-centre dataset, it may or may not represent whole region. Hence, multicentre prospective study would be advisable to draw stronger conclusions.

We conclude from the present study that patients with CN have almost threefold risk of mortality compared to individuals without CN. Prevalent coronary artery disease and low eGFR predict mortality in a given individual with CN. Patients with CN despite being younger have higher prevalence of micro-vascular complications at presentation.

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Author contributions AR was involved in conceptualising the study, prospective follow-up, clinical care of the patients, writing and editing the manuscript. SC analysed the data and wrote the initial draft of the manuscript. AB conceptualised the study and edited the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Institute Ethics Committee.

Informed consent A written and informed consent was obtained from all the participants of the present study.

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