Metwally *et al.*
Egypt J Neurol Psychiatry Neurosurg (2022) 58:151
https://doi.org/10.1186/s41983-022-00548-9

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

RESEARCH

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Assessment of intraepidermal nerve fiber density and neurophysiological studies in patients with idiopathic polyneuropathy

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Abstract

Background: Idiopathic polyneuropathy is an asymmetrical, length-dependent neuropathy in which neurophysiology demonstrates axonal damage involving large fibers, along with insidious onset and slow progression over 6 months, with no identified etiology in spite of thorough investigations. This study aimed to evaluate the diagnostic role of clinical, electrophysiological, and histopathological studies in patients with idiopathic polyneuropathy.

Methods: Case–control study included 20 patients with clinical and neurophysiological evidence of sensory or sensory–motor neuropathy with no apparent etiology after laboratory investigation were recruited from 127 patients with sensory–motor neuropathy of unknown etiology (the patients group). Twenty apparently healthy individuals, age- and sex-matched, with no neuropathy symptoms (the control group), were recruited from the Neurology Clinic of Al-Azhar University, Assuit.

Results: Age of onset of patients with idiopathic polyneuropathy (44–70) years, duration of illness (1–6) years, 60% had painful neuropathy, diagnostic neuropathic pain questioner (DN4 score) (5–7), abnormal pin brick (80%), abnormal vibration (90%), abnormal fine touch (75%), distal weakness (70%), and lost ankle reflex (90%). In the control group, there were substantial differences with respect to prolonged latency, diminished sympathetic skin response amplitude, and significant intraepidermal nerve fiber density reduction in skin biopsy cases. In diagnosing idiopathic polyneuropathy, the specificity and sensitivity of sympathetic skin response were (80–86)% and (81–89.5)%, respectively, whereas those of diminished intraepidermal nerve fiber density were (92.5%) and (97.5%), respectively.

Conclusion: The assessment of intraepidermal nerve fiber density had an important good diagnostic role in cases presented with polyneuropathy.

Keywords: Nerve conduction study, Sympathetic skin response, Intra-epidermal nerve fiber density

Introduction

Idiopathic polyneuropathy is a diagnosis of exclusion defined following neurologic examination, a comprehensive medical, laboratory testing, family history, as well as laboratory testing, with sensorimotor polyneuropathy or slowly progressive distal symmetric sensory and axonal degeneration on neurological clinical examination. Several studies have approached this topic in various ways. Richard Hughes characterized chronic idiopathic axonal polyneuropathy (CIAP) as late-onset, symmetrical peripheral neuropathy with late onset and unknown etiology [1].

Various terms, including chronic sensory polyneuropathy, CIAP, chronic polyneuropathy of undetermined

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cause, cryptogenic polyneuropathy neuropathy, and unclassified peripheral neuropathy, are used to describe idiopathic polyneuropathy [2].

Patients present with symmetrical, distal sensory and motor function loss in the lower extremities that extends proximally in a graded manner. The result is sensory loss in a stocking-like pattern, distal muscle weakness and atrophy, and loss of ankle reflexes [1].

In idiopathic neuropathy, initial sensory nerve amplitude loss occurs in a length-dependent manner, then loss of motor amplitudes and subsequent dissemination to the shorter nerve segments in the upper extremities. Later conduction velocities (CV) might be abnormal due to loss of the fastest conducting fibers or secondary demyelination [3, 4].

Electromyography (EMG) had positive waves and fibrillation potentials of very low amplitude, with few motor units of high amplitude and motor unit amplitude potential (MUAPs) that are 5–10 times the standard [5].

The sympathetic skin response (SSR) is a polysynaptic reflex produced by sweat glands' reflex activation via cholinergic sudomotor sympathetic efferent fibers. It was utilized for demonstrating the sympathetic nervous system derangement in multiple diseases, including peripheral neuropathies [6].

American Association of Neurology recommends fasting blood glucose, liver and renal function, serum vitamin B12, complete blood count, erythrocyte sedimentation rate, serum immunofixation electrophoresis, and thyroid function tests [7].

If there is a minimal clinical evidence of neuropathy, a skin biopsy may reveal degeneration of somatic unmyelinated fibers that transmit pain and temperature sensations that cannot be detected by normal neurophysiological testing [8, 9]. The hallmark of neuropathy is characterized by a decrease in intra-epidermal nerve fiber density (IENFD) in the distal leg [10].

Definite idiopathic sensory neuropathy necessitates decrease IENFD or abnormal sensory nerve conduction studies, e.g., nerve conduction velocity/sural sensory nerve action potential amplitude [3].

Follow-up skin biopsy revealed that IENF swellings are early markers of axonal degeneration, as well as a decline in IENFD predicts the transition to symptomatic neuropathy [11, 12].

Methods

The study was performed at the Department of Neurology, AL Azhar University Assuit, Egypt, from the beginning of April 2019 to the end of May 2021.

The ethical committee approved the study of the Faculty of Medicine, Al-Azhar University, Assuit. Written consent has been obtained from the participants.

This study is a randomized case–control study included 127 patients presented with bilateral symmetrical distal sensory or sensory–motor, autonomic (skin discoloration, change in skin temperature, sweating, change in blood pressure or heart rate) manifestation of polyneuropathy of unknown etiology with neurophysiological evidence of sensory or sensory–motor axonal or axonal demyelinating neuropathy etiology could be identified in 107 patients. In contrast, no etiology could be identified in 20 patients (having idiopathic polyneuropathy) and 20 apparently healthy individuals of sex- and age-matched as a control group.

Inclusion criteria

Patients who met the diagnostic criteria for idiopathic polyneuropathy include:

Symptoms

1. Altered sensation or loss of sensation begins in the distal extremities.
2. Symptoms present for at least 3 months.
3. No symptoms of weakness.
4. Symptoms of autonomic dysfunction and gait unsteadiness.

Signs

1. Sensory signs are symmetrically present in distal limbs, including any of the following: loss of proprioception, vibration, light touch, temperature, or pain (pinprick).
2. Areflexia or hyporeflexia might be present but is not necessary, even at the ankles.
3. Atrophy or minimal weakness in the distal muscles of toes and fingers.
4. Electrophysiology: motor and sensory–motor nerve conduction study (NCS), as well as needle EMG, are usually, but not invariably, abnormal. Abnormal findings denote a primarily axonal polyneuropathy.

Exclusion criteria

1. Any identifiable, toxic, metabolic, infectious, hereditary, or systemic disorder known to cause NCS and polyneuropathy abnormalities consistent with demyelination.

2. The presence of an underlying lymphoproliferative disorder, amyloidosis or malignancy is suspected if a monoclonal gammopathy is present.

3. Weakness on examination other than the mild toe and/or finger weakness.

All patients were subjected to:

1A: History taking and neurological history and examination.

1B: Application of (Douleur Neuropathique 4 questionnaire (DN4)) which consists of 10 items distributed across 4 questions, and the patient is asked to respond "yes" or "no" to each item; a "yes" response is assigned one point, while a "no" response is assigned zero points. The total score is out of ten; if the patient's score is equal to or greater than four points, it indicates that the patient suffers from neuropathic pain.

2: Blood tests including complete blood picture, 2-h glucose tolerance test or hemoglobin A1C, protein electrophoresis, thyroid function test, liver function test, kidney functions tests, vasculitic profile (chronic reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), rheumatoid factor (RF), virology screening (hepatitis C Virus antibody (HCV ab), anti neutrophil cytoplasmic antibody (ANCA), hepatitis B virus surface antigen (HBS ag), human immunodeficiency virus antibody (HIV ab). Furthermore, serum vitamin B12, anti-RO/SSA, vitamin B6, serum copper, and anti-LA/SSB were performed when Sjogren was suspected, as well as anti-tissue transglutaminase antibody (anti-TTG) for celiac disease when necessary.

Cerebrospinal fluid (CSF) aspiration and analysis: For patient groups only, including CSF cytology and chemistry when needed for searching infection, paraneoplastic and immune-mediated neuropathy.

3: Neurophysiological studies of patients and control groups include:

- Studies of the median ulnar, common peroneal, and posterior tibial nerves' motor nerve conduction
- F-wave response of median, ulnar tibial, and common peroneal nerves
- Sensory nerve conduction studies of the median, ulnar dorsal sural nerves
- Electromyography from tibialis anterior muscles for the presence of positive sharp wave, fibrillation or fibrillation activity at rest (denervation), and chronic neurogenic activity of large and complex MUPA with decreased recruitment with mild to moderate effort
- Sympathetic skin response from ipsilateral hand and foot following contralateral stimulation of median nerve at the wrist.

The following apparatus was utilized:

Nihon Kohden Corporation Model: MEB 2003k, Serial no. 00051, Japan 2012.

Recording electrodes: stainless steel surface electrode, 1.5 m, model NE-132B.

Stimulating electrodes: 20 mm; adult; MEB-92/9400 bipolar surface stimulating electrodes are used with poles about 20 mm apart.

EMG electrode 20 mm long, 0.45 dia, 2 electrode/set; NM131T.

4: Skin punch biopsy: 3-ml punch biopsy from 10 cm above the lateral malleolus of the distal leg from patients and controls after written consent and identification of intraepidermal nerve fiber density/mm using immunohistochemistry after stain with anti 9.5 protein gene antibody stain using (Leica microsystems Gmbh, Germany) full HD microscopic imaging system

Statistical analysis

The collected data were revised, coded, tabulated, and fed into a PC using the Statistical Package for Social Science (IBM Corp., released 2017 IBM SPSS Statistics for Windows, version 25.0. Armonk, NY: IBM Corp.). Data were presented, and suitable analysis was done according to the type of data obtained for each parameter. Descriptive statistics mean standard deviation (±SD) for numerical data frequency and percentage of non-numerical data. Student's t-test was used to assess the statistical significance of the difference between the two study group means, and the receiver operating characteristic (ROC)

Table 1 Demographic data of patients and controls

	Patients group	Control Group	*P* value
Age			
Mean ± (SD) Average	55.8 ± (7.5) years 45–71 years	54.3 ± (7.52) years 46–62 years	0.24
Sex	*N* (%)	*N* (%)	
Male Female	9(45%) 11(55%)	10 (50%) 10 (50%)	0.71
Marital status	*N* (%)	*N* (%)	
Married Not married	17(85%) 3(15%)	15(75%) 5(25%)	0.21
Residence	*N* (%)	*N* (%)	
Urbane Rural	12(60%) 8 (40%)	14 (70%) 6 (30%)	0.68

curve was used to evaluate the sensitivity and specificity of quantitative diagnostic measures

Results

Table 1 shows that mean age of idiopathic polyneuropathy in the present study is (55.8 ± 7.5 years), ranging between (45–71) years old, with female-to-male percent (55%- 45%), whereas the mean age of the control group is (50 ± 5.5) years old, ranging from (46–62) years, with a female-to-male ratio of 50–50%.

Table 2 shows that most of the patients had progressive painful neuropathy with predominant distal weakness and loss of ankle reflex and vibration sense at the ankle with little upper limbs affection.

Table 3 depicts significant differences between diminished compound motor action potential CMAP, slow motor conduction velocity NCV of both median and ulnar nerves In addition, there is a significant difference between patient and control groups in terms of diminished sensory potential amplitude and prolonged sensory distal latency DL of both sensory median and sensory ulnar nerves.

According to Table 4, there are substantial differences between patient and control groups with respect to prolonged DL, diminished CMAP, and slowing CV of both tibial and peroneal nerves. In addition, there are significant differences between patient and control groups in terms of prolonged DL and diminished sensory amplitude of the sural nerve.

Table 3 Comparison of motor and sensory nerve conduction study of upper limbs between patients having idiopathic polyneuropathy and control groups

		Patients *N* = 40 limb	Control *N* = 40 limb	*P* value
		Mean ± (SD)	Mean ± (SD)	
Median motor	DL (m s)	4.41 ± 1.05	3.6 ± 0.54	0.61
	CMAP (M v)	3.21 ± 2.03	4.2 ± 4.87	< 0.001
	NCV (m/s)	53.51 ± 1.53	62.1 ± 6.93	< 0.001
	F-wave (m s)	28.5 ± 4.5	27.3 ± 2.4	0.16
Median sensory	DL (m s)	3.2 ± 0.87	2.5 ± 0.39	0.043
	Amplitude (u.v)	7.9 ± 3.1	14.5 ± 3.2	< 0.001
Ulnar motor	DL (m s)	3.2 ± 3.6	2.99 ± 3.59	0.68
	CMAP (M.v)	5.33 ± 0.89	6.02 ± 0.65	0.038
	NCV (m/s)	54.8 ± 14.4	59.9 ± 4.54	0.034
	F-wave (m s)	27.3 ± 3.23	28.2 ± 2.62	0.17
Ulnar sensory	DL (m s)	2.67 ± 0.54	1.91 ± 0.22	0.031
	Amplitude (u.v)	3.7 ± 3.35	6.2 ± 3.22	< 0.001

DL: distal latency, CMAP (base to peak): compound motor action potential amplitude, NCV: nerve conduction velocity

Table 2 Clinical data in patients with idiopathic polyneuropathy

Age of onset	Mean: (52. ± 7) years Range:(44–70) years		Fasciculation		0%
			Proprioception *N* (%)		
Course			↓ Sense of position	4 (20)	20%
Progressive	16(20)	80%	↓ Sense of movement	4 (20)	20%
Stationary	4(20)	20%	↓ Vibration sense	18 (20)	90%
Duration	Mean ± SD: 3.08 ± (1.57) Range (1–6) years		↓ Fine touch	15 (20)	75%
Pain			Rombergism	7 (20)	35%
DN4 score	Mean ± SD: 5.6 ± (0.8) Range: (5–7)		Autonomic	5 (20)	25%
			Wasting LL	4 (20)	20%
	N (%)		Weakness UL	2 (20)	10%
Painful	12 (20)	60%	Weakness LL	14 (20)	70%
Painless	8 (20)	40%	Cranial *N*	0 (20)	0%
Reflexes in LL			Reflexes in UL		
↓ Ankle	18 (20)	90%	↓ Biceps reflex	2 (20)	10%
↓ Knee	11 (20)	55%	↓ Triceps reflex	0 (20)	0%
Pin brick LL			↓ Brachioradialis R	1 (20)	5%
Absent	6 (20)	30%	Pin brick UL		
Diminished	10 (20)	50%	Normal	16 (20)	80%
Normal	4 (20)	20%	Diminished	4 (20)	20%

R reflex, *UL* upper limb, *LL* lower limb, *DN4* Douler Neuropathique 4 questionnaire

Table 4 Comparison of motor and sensory nerve conduction study in the lower limbs in patients and controls

		Patients $N=40$ limb Mean ± (SD)	Control $N=40$ limb Mean ± (SD)	*P* value
Tibial motor	DL (m s)	5.9 ± 1.19	4.2 ± 0.54	< 0.001
	CMAP (MV)	6.51 ± 0.37	9.3 ± 4.7	< 0.001
	NCV(m/s)	41.2 ± 1.65	48.5 ± 1.86	0.001
	F-wave (m s)	49.6 ± 4.59	48.7 ± 3.69	0.29
Sural sensory	DL (m s)	4.08 ± 2.28	3.70 ± 1.26	0.031
	Amplitude (u.v)	6.7 ± 3.12	13.6 ± 4.6	< 0.001
Peroneal motor	DL (m s)	5.2 ± 1.47	4.19 ± 0.58	< 0.001
	CMAP (MV)	3.85 ± 2.35	5.7 ± 0.86	< 0.001
	NCV (m/s)	44.9 ± 6.24	48.2 ± 1.71	< 0.001
	F-wave (m s)	44.31 ± 7.59	44.89 ± 6.15	0.68

DL distal latency, *CMAP* (base to peak): compound motor action potential amplitude, *NCV* nerve conduction velocity

Table 5 Electromyography findings in patient groups

Electromyography findings in idiopathic polyneuropathy		
Findings	***N* (%)**	**Total**
Normal	2 (10%)	10%
Chronic neurogenic finding	12 (60%)	90%
Denervation	1 (5%)	
Chronic neurogenic finding + denervation	5 (25%)	

Table 6 Specificity and sensitivity of nerve conduction studies in patients with idiopathic polyneuropathy

Motor and sensory nerve conduction study in idiopathic polyneuropathy		
	Sensitivity	**Specificity**
Motor NCS	(47–76)%	(72–90)%
Sensory NCS	(42–83)%	(73–98)%
F-wave	(46–78)%	(50–95)%

NCS nerve conduction study

Table 5 illustrates that 90% of patients have abnormal EMG findings, with chronic neurogenic findings being the most prevalent.

Table 6 depicts the result of the ROC curve of sensory and motor nerve conduction studies between the two groups, demonstrating that the sensory nerve conduction studies are more sensitive compared to motor nerve conduction studies in diagnosing polyneuropathy.

According to Table 7, there are substantial differences between patient and control groups in terms of prolonged latency and diminished amplitude of sympathetic skin response from ipsilateral hand and foot.

In Table 8, the ROC curve of SSR demonstrated that sympathetic skin response had high sensitivity and specificity in early diagnosing neuropathy in patients despite nonapparent autonomic findings during the clinical evaluation of patients, with skin discoloration, sweating, change in blood pressure, and heart rate or evidence of gastrointestinal motility affection or genitourinary affection.

The intraepidermal nerve fiber density of patients with chronic idiopathic polyneuropathy is significantly lower than that of control groups, as depicted in Table 9.

Analysis of the ROC curve of patients with clinical and neurophysiological evidence of polyneuropathy of unknown etiology and control groups reveals in Table 10 that a decrease in intraepidermal nerve fiber density in distal leg punch biopsies has a sensitivity of 92.5% and a specificity of 97.5% in diagnosing polyneuropathy, with a cutoff value of 6.5/mm.

Discussion

Idiopathic polyneuropathy is an illness with sensory and motor disorders characterized by abnormal sensations of paresthesia, numbness, and pain in the feet and hands. There is no underlying cause for idiopathic polyneuropathy. Additionally, there may be muscle weakness in the feet and hands, problems with balancing, and walking difficulty in the dark or on uneven surfaces. A minority of the autonomic nervous system patients might be involved, and the patients may have vomiting, persistent nausea, diarrhea, incontinence, constipation, sweating, sexual dysfunction, or abnormalities [13].

Table 7 Comparison of sympathetic skin response of ipsilateral hands and foot in patients and controls

SSR		Patients $N=40$ side		Control $N=40$ side		*P* value
		Mean	± SD	Mean	± SD	
Hand	Latency m.s	2219.6	662.27	1306.6	264.5	< 0.001 S
	Amplitude m.v	1473.4	765.13	3538.1	1861.9	< 0.001 S
Foot	Latency m.s	2332.43	921.47	1313	455	< 0.001 S
	Amplitude m.v	1391.53	751.07	3194.8	1844.9	< 0.001 S

Table 8 Specificity and sensitivity of sympathetic skin response in chronic idiopathic polyneuropathy

Sympathetic skin response in idiopathic polyneuropathy		
	Sensitivity	**Specificity**
SSR	(81–89.5)%	(80–86)%

SSR sympathetic skin response

Table 9 Comparison of IENF density from distal leg 3-ml punch biopsy in patients and controls

	Patients ***N*** **= 20**		**Control** ***N*** **= 20**		***P*** **value**
	Mean	**± SD**	**Mean**	**± SD**	
IENFD (mm)	4.05	1.5	11.1	3.7	< 0.001

IENFD intra-epidermal nerve fiber density

Table 10 Specificity and sensitivity of intraepidermal nerve fiber density in chronic idiopathic polyneuropathy

Intraepidermal nerve fiber density in idiopathic polyneuropathy				
Marker	**Significance**	**Cutoff**	**Sensitivity**	**Specificity**
IENFD	< 0.001	6.5	92.5%	97.5%

IENFD intra-epidermal nerve fiber density

In the present study, the mean age of idiopathic polyneuropathy (55.8 7.5) years ranged from (45–71) years, with a male-to-female ratio of 55–45%, which provides information on the late onset of idiopathic polyneuropathy in both sexes. These findings are consistent with those of De Sousa [14] and Wolfe et al. [15], who found that the mean age of idiopathic poly neuropathy ranges between 51–63 years, as well as Lindh et al. [16], who found the incidence age is between (40–70) years, with slight female predominance.

In the present study, the age of onset was (52 ± 7) years, ranging between (44–70) years, which explains that patients complain after years from the onset of developing symptoms of neuropathy due to the slow progression, while the duration of illness (3 ± 1.6) years, ranging between (1–6) years and DN4 score is (5.6 ± 0.06) ranging between (5–7), which explains the slowly progressive course of the disease with the inability to diagnose easily because of the presence of these symptoms at old age without neuropathic feature. This finding agrees with Chiaramonte et al. [17], who found that the onset of idiopathic poly neuropathy (47.6 ± 12.6) years and duration of illness is (3.9 ± 3) years, and the DN4 score is 5.

The pain was reported in 60%, sensory loss in 20%, distal weakness in 70%, imbalance in 35%, and autonomic disorder in 25%, with no cranial nerve affection, suggesting that most of the patients had sensory–motor neuropathy without apparent disable weakness. This finding partially agrees with Pasnoor et al. [18], who found pain reported in 27–42%, sensory loss in 65%, distal weakness in 26–82%, and difficulty with balance in 33%.

There are substantial differences between diminished CMAP amplitude (< 0.001) and slow NCV (< 0.001) of both median and ulnar nerves with subclinical involvement of upper limbs despite no obvious abnormal motor findings in clinical examination. This finding is consistent with McLeod et al. [19], who found significant differences between NCV (0.001) and CMAP amplitude (< 0.001) of both median and ulnar nerve in patients with neuropathy of undetermined cause and control groups.

There are significant differences between diminished amplitude (< 0.001) and prolonged DL (0.043) of sensory median nerves and diminished amplitude (< 0.001) and prolonged DL (0.031) of both sensory ulnar nerves, indicating that sensory amplitude is sensitive early to axonal loss owing to collateral reinnervation and with a loss each remaining fiber conduct at its innate speed. Therefore, DL affected the extent of loss, which is compatible with McLeod et al. [19], who found significant differences between prolonged sensory latency (< 0.001) and diminished sensory amplitude (< 0.001) of both median and ulnar nerve in patients with neuropathy of undetermined cause and control groups.

There are significant differences between prolonged DL (< 0.001), diminished CMAP amplitude (< 0.001), and slowing NCV (< 0.001) of both tibial and peroneal nerves as in mild denervation collateral keep the number of muscle fibers high but with further axonal loss greater number of muscle fiber becomes denervated. CMAP amplitude falls and DL and NCV are affected by further degeneration [20], which correspond to the findings of McLeod. et al. [19], who found significant differences between slowing NCV (< 0.001) and diminished CMAP amplitude (< 0.001) of both tibial and peroneal nerves in patients with neuropathy of undetermined cause and control groups.

There is a substantial difference between prolonged LA and diminished amplitude of sural nerves and could be proven with McLeod et al. [19] found significant differences between prolonged sensory latency (0.001) and diminished sensory amplitude (0.001) of both median and ulnar nerve in patients with neuropathy of undetermined cause and control groups as neuropathy characterized by dying back. The phenomenon suggests that the sural nerve is affected earlier and more severely than the sensory upper limbs; consequently, significant differences between sural nerves can be expected.

Abnormal EMG activity was observed in 90% of patients with idiopathic polyneuropathy, and chronic neurogenic findings alone were observed in 60%, chronic neurogenic findings with denervation in 25%, and denervation activity alone in 5%. These results suggest motor axonal injury with evidence of reinnervation in a very slowly progressive course of polyneuropathy [5]. This finding is consistent with Lindh et al. [16] and Nusartha et al. [21], who found that 60% of patients with cryptogenic polyneuropathy had chronic neurogenic findings and 20% had chronic neurogenic findings with denervation. Even if idiopathic polyneuropathy is sensory or sensory–motor, this result suggests that motor nerves are subclinically involved.

In this study, the sensitivity of motor NCS is (47–76) % and sensory NCS (42–83)% and F-wave (46–78)% specificity of motor NCS (72–92) and sensory NCS (73–98) and F-wave (50–95)%. In contrast, Kelmenson et al. [22] found that motor NCS had "a sensitivity of (71–100%) "specificity of (82–96%)" sensory NCS had a sensitivity of (80–100%)" specificity of (31–54%) while Moss et al. [23] illustrated that sensitivity of motor NCS in lower limbs (LL) (88–100%)" specificity (63–85%) while the study in LL had sensitivity (88–100%) specificity (59–81%). The difference in study results is because this study showed the result in both upper and lower limbs.

There are significant differences between prolonged latency SSR (< 0.001) and diminished amplitude SSR (< 0.001) in both hand and foot between patients with idiopathic axonal polyneuropathy and control groups. Consequently, subclinical involvement of small nerve fiber can appear early even in the absence of autonomic symptoms in polyneuropathy [24], which aligns with lin et al. [25], who found significant differences in SSR latency of upper extremity (< 0.05) and amplitude of upper and lower extremity ($P < 0.05$) between patients with idiopathic axonal neuropathy and control groups.

In this research, sympathetic skin response in diagnosing autonomic neuropathy in patients with idiopathic polyneuropathy had sensitivity (81–89.5) % and specificity (80–86) %, which is compatible with Al-Moallem et al. [26] who found that SSR had a sensitivity of 87.5% and specificity 88.2% in diagnosing idiopathic sensory neuropathy and this could explain the presence of subclinical autonomic involvement even in absence autonomic symptoms.

There is a significant reduction of intraepidermal nerve fiber density at the distal leg ($P < 0.001$) between patients with chronic idiopathic polyneuropathy and control groups demonstrating selective degeneration of somatic unmyelinated nerve fibers conveying pain and thermal sensation cannot be observed in routine neurophysiological tests [27], aligning with Pittenger et al. [28] who found a significant reduction in IENF ($P < 0.001$) when comparing control subjects and patients groups in the distal leg of the patients with axonal polyneuropathy.

In this study, the sensitivity of IENFD in diagnosing CIAP is 92.5%, and specificity is 97.5%, indicating that the intra-epidermal nerve fiber density is a more reliable and sensitive factor in diagnosing neuropathy in patients who had little clinical and neurophysiological evidence of neuropathy [29]. This finding corresponds to the results obtained by Devigili et al. [30] and [31], who found that the sensitivity of IENF is 88% specificity is 89% in diagnosing idiopathic sensory polyneuropathy. In addition, it agrees with Chin et al. [32], who stated that IENF has a specificity of 95% and sensitivity of 80%.

Conclusions

In cases presenting with polyneuropathy, the intraepidermal nerve fiber density evaluation played a crucial diagnostic role.

Sympathetic skin response can detect autonomic dysfunction even in non-complaining patients.

Study limitation

- The current study has been conducted on a relatively small number of patients.
- Patients between the ages of 44–70 years, not younger, with difficulty in exclusion of hereditary neuropathy.
- Abnormal neurophysiological findings of neuropathic features were obtained in some non-complaining control subjects with old age.
- Some of the patients had normal neurophysiological findings despite apparent clinical findings.
- Obtaining skin biopsy from healthy subjects because of non-available reference IENFD in the studied community.

Recommendations

- Studying skin biopsy in a large number of patients in different countries to find the international variable value of IENFD in different genders and populations.
- Studying the intraepidermal nerve fiber density in diagnosing polyneuropathy is essential because of the conflict between neurophysiological findings in diagnosing neuropathy at older ages.
- Follow-up with intraepidermal nerve fiber density can be used in follow-up the progression of polyneuropathy and response to medical treatment.

Abbreviations
IENFD: Intraepidermal nerve fiber density; SSR: Sympathetic skin response; LL: lower limbs; UL: Upper limb; NCS: nerve conduction study; EMG: Electromyography; DN4: Douler Neuropathique 4; CIAP: Chronic idiopathic axonal polyneuropathy; DL: Distal latency; CMAP: Compound motor action potential; NCV: Nerve conduction velocity; MUPA: Motor unite potential amplitude; CSF: Cerebrospinal fluid; ESR: Erythrocyte sedimentation rate; CRP: Chronic reactive protein; ANA: Antinuclear Antibody; ANCA: Anti neutrophil cytoplasmic antibody; HCV: hepatitis C virus; HIV: human immunodeficiency virus; HBS Ag: hepatitis B virus surface antigen; Anti TTG: Anti tissue transglutaminase; R: Reflex.

Acknowledgements
We thank all the participants and the technical workers for their help and support though out the study.

Authors contributions
MM and NA designed the research study. HA and MM performed the research. AF and KS provided help and advice on the patient selection. MA provided histopathological preparation and analysis. HA and MM analyzed the data. MM and HA wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Funding
The authors did not receive any funding for this research.

Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the ethics committee of research involving human subjects of faculty of medicine Al-Azhar University, Assuit branch. Written consent was obtained from each individual before being enrolled in the study.

Consent for publication
Not applicable.

Competing interests
None of the authors has any competing interests.

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Received: 28 October 2021 Accepted: 9 September 2022
Published online: 09 December 2022

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