Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (6) Issue (5) Part (1) (2021), (9-14) **online: ISSN 2356–976x**
http://bjas.journals.ekb.eg

Study of Patients having Idiopathic Polyneuropathy

N.A.Metwally[1], M.M.Hasan[1], M.A.Ali[2] and H.A.Abd- Elsalam[1]
[1]Neurology, Dept., Faculty of Medicine, Al-Azhar Univ., Assuit, Egypt
[2]general pathology, Dept., Faculty of Medicine, Al-Azhar Univ., Assuit, Egypt
E-mail: Dr_ha100@yahoo.com

Abstract

Background: Chronic idiopathic polyneuropathy is asymmetrical, axonal damage involving large fibres of insidious onsets is disclosed in neurophysiologic long-dependent neuropathy and slowly progressive course over a minimum of six months without aetiology can be identified despite the appropriate investigations. This research was designed to investigate idiopathic polyneuropathy individuals. Methods: The comparative patient control research comprised 20 patients selected from 127 polyneuropathic and 20 matching age or sex controls from the Al-Azhar University Neurology Clinic at Assuit Hospitals, April 2019 to May 2021. Results: Age of onset of idiopathic polyneuropathy patients (47-73), length of disease (1-6) years (60%), DN4 score (5–7), abnormal pine brick (80%), abnormal vibrations (90%), abnormal fine touch (75%), distal weaknesses (70%) losing ankle (90%) and wasting (20 percent). This represents significant variations in the amplitude of decreased motor-action compounds and the reduced speed of median,ulnar, tibial peroneal nerves across the tested groups. Significant variations between tibial and peroneal tissues are also seen in prolonged distal latency, decreased sensory amplitude and extended latency between sensory (median, ulnar, and sural) nerves. The delay differences and a reduced amplitude of sympathetic cutaneous response across the investigated groups are significant. There are also substantial differences in the intraepidermal nerve fibre density decrease in skin biopsy from the distal leg between idiopathic polyneuropathical patients and control groups. Conclusion: Intraepidermal nerve fibre density in skin biopsy is responsive to idiopathic polyneuropathy than standard neurophyological investigations.

Keywords: Sympathetic skin response, Intra epidermal nerve fiber density and NCS.

1. Introduction

The diagnosis of exclusion is chronic idiopathic axonal polyneuropathy based on a thorough medical, family history, neurological examination and laboratory tests. Patients are expected to have neurological clinical examination with slowly progressing distal symmetric sensory or sensory-motor polyneuropathy and neurophysiologic axonal degeneration. [1]. Terms include idiopathic polyneuropathy, including chronic idiopathic axonal polyneuropathy (CIAP), chronic sensory polyneuropathy, unknown aetiology chronic polyneuropathy, undifferentiated peripheral neuropathy, and crypogenic polyneuropathy [2].

The median onset age in individuals with chronic idiopathic axonal polyneuropathy is between 55 and 63 years [3, 4].

Idiopathic polyneuropathy is an underlying dying-back neuropathy, which spreads closely with symmetrical, distal loss of motor and sensory function in the lower limbs. The consequence is sensory loss in a pitch pattern, weakness and distal muscular atrophy with loss of knee reflexes [1].

Early sensory nerve amplitude loss follows a loss of motor amplitudes with progressive l propagation in upper limbs in idiopathic sensory or sensory neuropathy. Speeds may be aberrant due to secondary demyelination, or loss of the fastest conducting fibre of the nerve, after severe diseases [3, 5].

The electromyography shows positive waves and fibrillation potential of very low amplitude in patients with idiopathic Neuropathy; motor units are not numerical and of high amplitude but are not complex as there is sufficient time to simplify the wave and motor-unit action potential is 5 to 10 times as normal. The degree of denervation may be evaluated with the EMG needle [6], the proximal muscle.

The sympathetic skin response (SSR) is a polysynaptic reflex that results from reflex activation of sweat glands by sympathetic sympathetic cholinergic sudomotor fibres. It utilised to demonstrate a sympathetic affection of the nervous system in a broad range of illnesses that may influence peripheral neuropathy and other conditions [7].

Parameters for the laboratory test in distal symmetric polyneuropathy have been published by the American Neurology Association, and parameters recommend the following tests: rapid blood glucose, renal and liver function, complete blood count/deferential blood count, B12 sedimentation rate of serum vitamin B, thyroid hormone or thyroid function tests, and serum electron immunophixing tests.

Skin Biopsy is a good diagnostic test in individuals with neuropathy symptoms.

The specific degeneration of somatic unmyelinated fibres that transmit pain and heat sensations may be shown by skin biopsy. The neurophysiological standard tests cannot detect these fibres. Diagnostic information may even be provided if there is little or no clinical indication of neuropathy. Also used to assess neuropathy progression[9, 10].

It has been shown that intra-epidermal nerve fibre density is helpful to confirm the diagnosis of peripheral neuropathy of different etiologies with specificities ranging from 95% to 97%, sensitivity ranging from 45% to 80% [11].

The characteristic to identify neuropathy is a decrease in the IENF density (number of fibres per linear mm) at the distal leg[9]. Increased IENFs were observed in individuals with neuropathy and may be early markers of nerve fibre dysfunction[14].

Follow-up skin biopsy has shown that the IENF inflammation is an early sign for axonal degradation and that the IENF density decrease predicts a transition to symptomatic neuropathy[15].

Definite diagnosis of idiopathic sensory neuropathy requires aberrant sensory nerve conduction studies, e.g. potential sural sensory nerve action amplitudes and/or nerve conduction velocity (NCV) or reduced intraepidermal fibre density; (IENFD). Sensory Nerve Conductivity and IENFD were selected as the two DSP diagnostic tests because they detect anomalies in big and small sensory neurons and they have accessible age-based normative values for detecting abnormal cases [3].

2. Patients and methods.

This study was a case-control study. Included 20 patients with idiopathic polyneuropathy recruited from 127 patients with polyneuropathy, 20 healthy individuals of matched age and sex as a control group. All patients were recruited from the outpatient clinic of Neurology department of Al-Azhar University, Assuit branch.

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

All patients were subjected to

1. Full history taking; complete clinical examination and applying diagnostic neuropathic pain questioner score (DN4 score).
2. **Blood tests:** Including (Complete blood picture, 2hours glucose tolerance test or hemoglobinA1C, Protein electrophoresis, Immunoglobulin IGg, IGA and IGM. Serum vitamin B12, vitamin B6, serum copper, Thyroid function test, liver function test (ALT and AST) Kidney functions tests (serum creatine and BUN). Vasculitic profile (ESR, CRP, ANA, RF, ANCA), Virology screening for (HCV ab, HBSag, HIV ab), Anti RO/SSA and Anti LA/SSB antigen antibodies, Anti TTG and CSF aspiration and analysis.
3. **Neurophysiological studies of patients and control groups**: include.
   - Motor nerve conduction studies of Median , ulnar, common peroneal and posterior tibial nerves
   - F wave response of Median , ulnar tibial and common peroneal nerves
   - Sensory nerve conduction studies of the median , ulnar dorsal sural nerves
   - Electromyelography from tibialis anterior muscles.
   - Sympathetic skin response from ipsilatral hand and foot after contralateral stimulation of median nerve at wrist.
4. **Skin punch biopsy:** 3ml punch biopsy from 10 cm above the lateral malleolus of distal leg and identification of intra epidermal 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.
5. **Statistical analysis**

The collected data was revised, coded, tabulated and introduced to a PC using 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. Shapiro test was done to test the normality of data distribution. Analytical statistics: Student T Test was used to assess the statistical significance of the difference between two study group means.

3. Results

The present study included 20 patients with idiopathic polyneuropathy recruited from 127 patients presented with polyneuropathy and 20 healthy control subjects of matched age and sex.

Table (1) Demographic data of studied groups.

		Patient group	Control group
Age	**Mean**	55.8±7.5 years	50±5.5 years
	Average	47-73 years	46-62 years
Sex	**Male**	9(45%)	10(50)
	Female	11(55%)	10(50%)
Marital Status	**Married**	17(85%)	15(75%)
	Not married	3(15%)	5(25%)
Residence	**Urbane Rural**	12(60%)	14 (70%)
		8(40%)	6 (30%)

This table showing that mean age incidence of idiopathic polyneuropathy in our study is (55.8 ±7.5 years old), range between (45-71) years old with female to male percent (55 % - 45%). while mean age of control group is (50±5.5) years old range between (46-62) years and male to female percent (50%-50%) Table (1).

Table (2) Clinical data in patient with idiopathic polyneuropathy.

Age of onset	Mean: (55.8±7.5) years Range :(47-73) years		**Fasciculation**		0 %
	Course		**Propreception**		
Progressive	16(20)	80%	↓ Sense of position	4(20)	20%
Stationary	4(20)	20%	↓ Sense of movement	4(20)	20%
Duration	Mean: (3.08±1.57) years Range (1 - 6) years		↓ Vibration sense	18(20)	90%
	Pain		↓ Fine touch	15(20)	75%
DN4 score	Mean: (5.6±0.8) Range : (5 - 7)		**Romborgism**	7 (20)	35%
			Autonomic	5 (20)	25%
			Wasting LL	4(20)	20%
			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 R	2(20)	10%
↓ **Knee**	11(20)	55%	↓ Triceps R	0(20)	0%
	Pin brick LL		↓ Brachioradialies 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%

This table represent that almost of the patients had age of onset between 47- 37 years old and most of patients with idiopathic polyneuropathy in our study had progressive painful sensory course with predominant distal weakness in lower limbs and loss of ankle reflex and vibration sense at ankle with little upper limbs affection without cranial nerve affection and neuropathic diagnostic pain score is between (5 -7) Table (2).

Table (3) Comparison of motor and sensory nerve conductionm study at upper limbs in studied groups.

		Patients N=40 limb		**Control N=40 limb**		**P-Value**
		Mean	**±SD**	**Mean**	**±SD**	
Median motor	**DA (m.sec)**	4.41	1.05	3.6	0.54	<0.67(NS)
	CMAP (M.v)	3.21	2.03	4.2	4.87	<0.001(S)
	NCV (m/sec)	53.5	11.53	62.1	6.93	<0.001(S)
Median sensory	**F (m.sec)**	28.5	4.5	27.3	2.4	0.16 (NS)
	LA (m.sec)	3.2	0.87	2.5	0.39	0.043(S)
	AMP (u.v)	7.9	3.1	14.5	3.2	<0.001(S)
Ulnar motor	**DL (m.sec)**	3.2	3.6	2.99	3.59	0.68 (NS)
	CMAP (M.v)	5.33	0.89	6.02	0.65	0.038(S)
	NCV (m/sec)	54.8	14.4	59.9	4.54	0.034(S)
Ulnar sensory	**F m.sec**	27.3	3.23	28.2	2.62	0.17 (NS)
	LA (m.sec)	2.67	0.54	1.91	0.22	<0.001(S)
	AMP (m.v)	3.7	3.35	6.2	1.22	<0.001(S)

This table shows that ther is significant differences between compound motor action potential (CMAP), motor conduction velocity (NCV) of both median and ulnar nerves. Ther is significant differences of sensory action potential amplitude (SAPA) and sensory latency (LA) of both sensory median and sensory ulnar nerves between patient and control groups Table (3).

Table (4) Comparison of motor and sensory nerve conduction study in the lower limbs of studied groups.

		Patients N=40 limb		Control N=40 limb		P-Value
		Mean	±SD	Mean	±SD	
Tibial motor	DA (m.sec)	5.9	1.19	4.2	0.54	<0.001(S)
	CMAP (MV)	6.51	0.37	9.3	4.7	<0.001(S)
	NCV(m/sec)	41.2	1.65	48.5	1.86	0.01 (S)
	F(m.sec)	49.6	4.59	48.7	3.69	0.27 (NS)
Sural sensory	LA (m.sec)	4.08	2.28	3.70	1.26	0.031 (S)
	SAMP (uv)	6.7	3.12	13.6	4.6	<0.001(S)
Peroneal motor	DA (m.sec)	5.2	1.47	4.19	0.58	<0.001 (S)
	CMAP (MV)	3.85	2.35	5.7	0.86	<0.001(S)
	NCV (m/sec)	48.2	6.24	44.9	1.71	<0.001(S)
	F(m.sec)	44.31	7.59	44.89	6.15	0.68(NS)

This table showed that ther is significant differences between motor distal latency (DL), compound motor action potential amplitude (CMAP), motor conduction velocity (CV) of both tibial and peroneal nerves between patient and control groups. Also ther is significant differences of sensory latency, sensory potential amplitude (SAPA) of sensory sural nerve between patient and control groups Table (4).

Table (5) Comparison of SSR of hands and foot in patient having idiopathic polyneuropathy and control group.

		Patients N=40 side		Control N=40 side		P-Value
		Mean	±SD	Mean	±SD	
Hand	LA m.sec	2216.6	672.27	1406.6	164.5	<0.001 S
	AMP MV	1574.4	565.13	3632.1	1861.9	<0.001 S
Foot	LA m.sec	2131.41	711.47	1413	515	<0.001 S
	F m.sec	1311.53	741.07	3094.8	1644.9	<0.001 S

This table shows significant differences of prolonged latency and diminished amplitude of sympathetic skin response ipsilatral hand and foots between patient with chronic idiopathic polyneuropathy and control group Table(5).

Table (6) Comparison of intra epidermal nerve fiber density density from in patients and control groups .

	Patients N=20		Control N=20		P-Value
	Mean	±SD	Mean	±SD	
IENF (mm)	6.15	1.25	12.2	3.57	<0.001 S

This table shows that there is significant marked reduction of intraepidermal nerve fiber density in patients with chronic idiopathic axonal polyneuropathy compared with control groups Table (6).

4. Discussion

Cryptogenic polyneuropathy is an exclusion diagnosis based on thorough medical, family history, neurological exams and laboratory tests[1].

In this study the mean age of idiopathic polyneuropathy (55.8±7.5), which range from the (47-73) year to the (55 percent-45 percent) male to female ratio, is agreed with De Sousa., (2006)[17] and Wolfe et al., (1999)[17] which found that mean age of idiopathic polyneuropathy (51-63) and is also in agreement with Janose T et al., (2005)[19] who found the mean age of idiopathic polyneuropathy (51-63) years)

In the current research, we discovered that pain was found to be 60%, sensory loss at 20%, distal weakness at 70%, 35% and the autonomy at 25%, whereas Pasnoor, and others (2013)[20] who found pain reported at 27% to 42%, sensory loss at 65%, distal weakness of 26% to 82%, and balance difficulties at 33%.

This is consistent with Mc Leod., et al. (1984)[21] who observed that ther are substantial disparities of both the median and ulnal nerve amplitude between NCV (0.001) and CMAP (>0.001) of both medium and ulnar in patients with undefined origin and control neuropathia.

Sensory differences between sensory amplitude (<0.001) and latency (<0.001) are significant in both median and ulnar nerves and agree with Mc Leod., et al (1984)[21] who found that ther differences between medial and ulnar nerve latency(<0.001) and

SAPA(<0.001) are significant in patients with undetermined causal and control group neuropathy.

The latency (< 0.001), the Compound Motor action Potential (CMAP) amplitude (< 0.001) and the conductor velocity (CV) of both tibial and peroneal nerves are significantly different, and McLeod. et al.(1984)[21] found that there are significant CV (< 0.001) and CMAP (<0.001) differences of the tibial and peroneal nerves i. Their differences are significant.

Ther were significant differences between sensory latency (LA) (0.031) and sensory amplitude (SAPA (<0.001) of sural nerves, and this was proven by the McLeod., et al. 1985) (21) who found that ther was significant differentiation between median and ulnar nerve latency (<0.001) and latency of the SAPA (<0.001).

This was consistent with Situ J et Al., (2012)[22] that found significant differences between SSR upper-extreme latency and upper- and lower-extremity amplitude (P < 0.05) between patients with prolonged latency SSR (< 0.001) and decreased amplitude SSR (< 0.001) in their hands and foot between patients with idiopathic axonal polyneuromas and control groups.

This is a significant reduction in intraepidermal nerve fibre density at distal leg (P<0.001) between chronic idiopathic polyneuropathy patients and control groups and is in agreement with Pittenger et al, (2004).[23] It was found that the IENF decrease (P<0.001) was significant by comparing controls with axonally polyneuropathic patient's distal leg groups.

5. Conclusion

Decreased intra-epidermal nerve fibre density in distal leg skin biopsy is regarded a simple and accurate idiopathic polyneuropathy diagnostic test.

References

[1] Group, IndINeP StudyBurden of neuropathic pain in Indian patients attending urban, specialty clinics: results from a cross sectional study. Pain Practice.vol.8(5),pp.362-378,2008.

[2] Singer, A.Mike, Vernino, A.Steven, & Wolfe, I. Gil Idiopathic neuropathy: new paradigms, new promise. Journal of the Peripheral Nervous System.vol.17,pp. 43-49,2012.

[3] Freeman, Roy, Gewandter, S.Jennifer, Faber, G.Catharina, Gibbons, Christopher, Haroutounian, Simon, Lauria, Giuseppe, . . . Smith, A Gordon Idiopathic distal sensory polyneuropathy: ACTTION diagnostic criteria. Neurology.vol.95(22),pp.1005-1014,2020.

[4] Grant, Ian ACryptogenic sensory polyneuropathy. Peripheral neuropathy.vol.15,pp.2321-2333,. 2005.

[5] Gooch, L.Clifton, & Weimer, H.Louis The electrodiagnosis of neuropathy: basic principles and common pitfalls. Neurologic clinics.vol.25(1),pp.1-28,2007.

[6] Bromberg, B.Mark An electrodiagnostic approach to the evaluation of peripheral neuropathies. Physical Medicine and Rehabilitation Clinics.vol.24(1),pp.153-168,2013.

[7] D. Claus, & R. Schondorf, Sympathetic skin response. The international federation of clinical neurophysiology. Electroencephalography and clinical neurophysiology. Supplement.vol. 52,pp.277-282,1999.

[8] JD. England, GS.Gronseth, , G. Franklin, GT. Carter, LJ.Kinsella, , JA.Cohen,Latov, NPractice Parameter: The Evaluation of Distal Symmetric Polyneuropathy: The Role of Laboratory and Genetic Testing (An Evidence-Based Review) Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. PM&R.vol.1(1),pp.5-13,2009.

[9] Nolano, Maria, Tozza, Stefano, Caporaso, Giuseppe, & Provitera, Vincenzo. Contribution of skin biopsy in peripheral neuropathies. Brain Sciences.vol.10(12),pp.989,2020.

[10] Lauria, Giuseppe, & Devigili, GraziaSkin biopsy as a diagnostic tool in peripheral neuropathy. Nature clinical practice Neurology.vol.3(10),pp.546-557,2007.

[11] Timar, Bogdan, Popescu, Simona, Timar, Romulus, Baderca, Flavia, Duica, Bogdan, Vlad, Mihaela, Simu, MihaelaThe usefulness of quantifying intraepidermal nerve fibers density in the diagnostic of diabetic peripheral neuropathy: a cross-sectional study. Diabetology & metabolic syndrome.vol.8(1),pp.1-7,2016.

[12] McArthur, C.Justin, E.Stocks, Adelaine, Hauer, Peter, Cornblath, R.David, & Griffin, W.John Epidermal nerve fiber density: normative reference range and diagnostic efficiency. Archives of neurology.vol.55(12),pp.1513-1520,1998.

[13] Lauria, Giuseppe, Bakkers, Mayienne, Schmitz, Christoph, Lombardi, Raffaella, Penza, Paola, Devigili, Grazia, Umapathi, Thirugnanam. Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. Journal of the Peripheral Nervous System.vol.15(3),pp.202-207,2010.

[14] G.Wendelschafer-Crabb, Kennedy, R.William, & Walk, David. Morphological features of nerves in skin biopsies. Journal of the neurological sciences.vol.242(1-2),pp.15-21,2006.

[15] Themistocleous, Andreas C, Ramirez, Juan D, Serra, Jordi, & Bennett, David LH. The

clinical approach to small fibre neuropathy and painful channelopathy. Practical neurology.vol.14(6),pp.368-379,2014.

[16] Herrmann, N.David, McDermott, P.Michael, Henderson, Don, Chen, Lin, Akowuah, Kwame, Schifitto, Giovanni, & Consortium, North East Aids DementiaEpidermal nerve fiber density, axonal swellings and QST as predictors of HIV distal sensory neuropathy. Muscle & nerve.vol. 29(3),pp.420-427,2004.

[17] EA.De Sousa, AP.Hays, RL,Chin, , HW,Sander, & TH.Brannagan.Characteristics of patients with sensory neuropathy diagnosed with abnormal small nerve fibres on skin biopsy. Journal of Neurology, Neurosurgery & Psychiatry.vol.77(8),pp.983-985,2006.

[18] Wolfe, I.Gil, Baker, S.Noel, Amato, A.Anthony, Jackson, E.Carlayne, Nations, P.Sharon, Saperstein, S.David, Barohn, J. Richard Chronic cryptogenic sensory polyneuropathy: clinical and laboratory characteristics. Archives of neurology.vol. 56(5),pp.540-547,1999.

[19] Lindh, Jonas, Tondel, Martin, Österberg, Anders, & Vrethem, Magnus. Cryptogenic polyneuropathy: clinical and neurophysiological findings. Journal of the Peripheral Nervous System.vol.10(1),pp.31-37,2005.

[20] Pasnoor, Mamatha, Nascimento, JM.Osvaldo, Trivedi, Jaya, Wolfe, I.Gil, Nations, Sharon, Herbelin, Laura, Dimachkie, Mazen. North America and South America (NA-SA) neuropathy project. International Journal of Neuroscience.vol. 123(8),pp.563-567,2013.

[21] JG.McLeod, , RR.Tuck, JD.Pollard, J.Cameron, & JC.Walsh, Chronic polyneuropathy of undetermined cause. Journal of Neurology, Neurosurgery & Psychiatry.vol.47(5),pp.530-535,1984.

[22] Situ, Jie, Wu, Jian, JL.Wang, , DX.Zhu, , JJ.Zhang, , WW.Liu, & ZH. Qin, A study of sympathetic skin response to the damage of autonomic nerves function in patients with chronic N-hexane poisoning. Zhonghua lao dong wei sheng zhi ye bing za zhi= Zhonghua laodong weisheng zhiyebing zazhi= Chinese journal of industrial hygiene and occupational diseases.vol.30(5),pp.339-342,2012.

[23] Pittenger, L.Gary, Ray, Madhumita, Burcus, I.Niculina, McNulty, Patricia, Basta, Baher, & Vinik, I.Aaron Intraepidermal nerve fibers are indicators of small-fiber neuropathy in both diabetic and nondiabetic patients. Diabetes Care.vol.27(8),pp.1974-1979,2004.