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RESEARCH

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Sensitivity of non-conventional electro-diagnostic techniques to detect neuropathy in patients with hepatitis "C" viral infection

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Abstract

Background Hepatitis "C" virus (HCV) infection has become a growing global health concern. Chronic HCV infection is usually accompanied by extra-hepatic manifestations. Peripheral neuropathies are the most common neurological complications. Electrophysiological tests play an important role in diagnosing polyneuropathy and identifying its pathophysiology. This study aimed at highlighting the sensitivity of non-conventional, quantitative, electrophysiological techniques in the detection of neuropathy in patients having HCV infection. Forty-five HCV patients were recruited for this study. Conventional motor and sensory conduction studies (NCS) were initially performed followed by interference pattern analysis (IPA). Two quantitative nerve conduction scores were also studied: motor amplitude score (MAS) and sensory amplitude score (SAS).

Results In the two patients' subgroups (having numbness versus having no numbness), MAS showed a significant difference, while the SAS showed a non-significant difference. In the two subgroups (with normal NCS versus those with abnormal/suspected NCS), the MAS and the SAS mean values were significantly different. Also, there was a positive significant correlation found between the IPA mean amplitude and the SAS parameter. Finally, we presented the results of the diagnostic performance of the MAS and the SAS in detecting abnormal NCS.

Conclusions MAS and/or SAS scores could be used as good screening tools for the detection of neuropathy. We here recommend expanding the non-conventional NCSs to other etiologies of polyneuropathy.

Keywords Motor amplitude score (MAS), Nerve conduction studies (NCS), Neuropathy, Quantitative techniques, Sensory amplitude score (SAS)

Background

Hepatitis "C" virus (HCV) infection has become a growing global health concern, with more than 71 million being affected. It is also responsible for 400,000 deaths annually [1]. The World Health Organization (WHO) assumes that 1.1% of the global population is affected, with a vast geographic distribution and suspected underestimation. Subclinical infections are dynamic and asymptomatic for years [2].

Egypt was one of the countries with the highest prevalence of HCV infection, having about 5.5 million viremic patients. This prioritized the national health plan for HCV eradication [4]. Egyptian Demographic and Health Surveys (EDHS) measured antibody prevalence among the adult population aged 15–59 years. It was estimated to be 14.7% in 2009 and 10.0% in 2015. Egypt has the highest HCV prevalence in the world,

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with 7% of adults (15–59 years old) HCV RNA positive [3]. Those percentages were apparently higher than the global ones [5].

Chronic HCV infection is usually accompanied by extra-hepatic manifestations that increase morbidity and mortality and worsen quality of life. This may even contraindicate antiviral therapy. Peripheral neuropathies are the most common neurological complications. Its prevalence is up to 86% of the infected patients with, and 43.5% of those without cryoglobulinemia [2].

Several hypotheses in the literature regarding the pathogenic role of liver disease in the genesis of neuropathy have been postulated. Although, the pathogenesis is not well known, there could be different mechanisms of nerve damage, including the liver failure itself, the specific etiology of the liver disease, and the frequent comorbidities [6].

Electrophysiological tests play an important role in diagnosing polyneuropathy and identifying its pathophysiology [7]. Conventional nerve conduction studies (NCS) are used to study the affection of large fibers of the motor and the sensory nerves [8].

One of the non-conventional quantitative electromyography (EMG) methods is the IPA, with turns and amplitude cloud. It was first introduced by Stålberg and coworkers in 1983[9]. It encompasses recording the interference pattern signal from six to ten different sites of the examined muscle, with a plot of the mean amplitude (MA) versus number of turns (NT) comprising more than 90% of data points in normal individuals. The boundary of this area is named "the normal cloud" [10].

The concept of quantitative scores including composite NCS rather than individual nerves has been introduced. Those scores are believed to have higher sensitivity than the individual NCS. This concept had been implemented extensively in diabetic polyneuropathy. Dyck and colleagues conducted a study in 2003 on diabetic patients, they found that the sensitivity of composite scores were 41.7% versus 2.8% when individual NCS were used [11].

A continued step forward was accomplished by Drunker and colleagues in 2021, where they incorporated several NCS into Z-compounds. They studied the sensitivity of different combinations to reach a conclusion that combining studies of five nerves namely, peroneal, posterior tibial, sural, medial planter and superficial peroneal nerves yields high sensitivity in diagnosing diabetic polyneuropathy [12].

This study was conducted to highlight the sensitivity of non-conventional, quantitative, electrophysiological techniques in the detection of neuropathy in patients having HCV.

Methods

This prospective cross-sectional study had the approval of the Ethics Committee for research of the Faculty of Medicine—Cairo University (MS-88 2019) with clinical trial registration number (NCT04340999). A written informed consent was taken from each patient. Patients' personal data were hidden.

Forty-five HCV patients were recruited for participation in this study, from August 2018 to December 2019. Their diagnosis was made by the assessment of HCV antibodies, some of which were accidently discovered during a national HCV campaign; that was held in Egypt. Both genders were included, and the age window was between 30 and 60 years.

Patients were assessed neurologically, examined by pelvic-abdominal ultrasound and blood samples were withdrawn for laboratory tests. Complete blood count, liver function, kidney function, serum albumin, glycosylated hemoglobin, and coagulation profile were done to exclude patients with other causes of peripheral neuropathy (such as diabetes mellitus and renal disease).

The international functional classification of chronic liver disease named "Child–Pugh" is used to assess the severity of liver affection. It is based on the presence of jaundice, ascites, encephalopathy, in addition to the serum albumin concentration, and the prothrombin time. The total score classifies patients into grades A, B, or C [13].

Electrophysiological studies were accomplished on the Natus Viking EMG machine (Viking Quest system with software V7.4; Nicolet Biomedical, Madison, Wisconsin, USA), 672-003800 REV.08. NCS both motor conduction studies (MCSs) and sensory conduction studies (SCSs) were initially performed. The left ulnar, right deep peroneal, and left posterior tibial nerves were studied in MCSs. The SCSs were performed for the left ulnar and the right sural nerves using surface recording electrodes. The studies were carried out following techniques mentioned by Preston and Shapiro, 2013[14].

According to a recent review of existing guidelines for peripheral neuropathy diagnosis, by Tankisi and colleagues in 2020, it was suggested by the presence of one abnormal parameter in at least two different nerves and one of them being the sural nerve. Hence, we adopted our research criteria. The patients fulfilling those criteria are having abnormal NCSs [15]. We also assumed that the patients having abnormal sural sensory nerves (which were only two patients) had suspected results.

Two quantitative nerve conduction scores were studied: motor amplitude score (MAS) and sensory amplitude score (SAS). The SAS is the resultant ratio of dividing the sum of amplitudes of both the ulnar and sural sensory nerves of the studied subjects by their reference normal

values as mentioned by Preston and Shapiro, 2013 [14]. The MAS was calculated likewise, but for the ulnar and the peroneal nerves [6].

The IPA was done using a concentric needle electrode of 5 cm length and 300 uV recording diameter. It was inserted in the abductor digiti manus muscle, according to the technique of Preston and Shapiro, in 2013 [14]. The subject, then, was instructed to gradually increment the contraction force, from minimum to maximum, roughly over 10 s (variable from 7 to 10 s). The muscle electrical activity is sampled in 5 different sites of it. The captured electrical signal is analyzed every 100 ms. The parameters obtained include NT, MA, and Turns/amplitude ratio. A plot of MA versus NT is obtained [16, 17].

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation, median, minimum, and maximum for quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test. For comparisons of the categorical data, the Chi-square ($\chi 2$) test was performed. The exact test was used instead when the expected frequency was less than 5. Correlations between quantitative variables were done using the Spearman correlation coefficient. A *P*-value less than 0.05 was considered statistically significant. Finally, ROC curve analysis was performed to assess the diagnostic performance of the MAS and the SAS in detecting abnormal NCS. All those tests were done using this software IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.

Results

Patients were recruited from the internal medicine and the endemic outpatient clinics in Kasr Alainy Hospital. They had a mean age of 52.07 ± 7.44 years. Most of the studied participants were males 80% (36/45). According to the clinical evaluation of the recruited patients, 31(68.9%) patients had Child–Pugh "A" classification, while Child–Pugh "B" and "C" account for 24.4 (11/45) and 6.7% (3/45), respectively.

Following the definite presence of numbness in the given history, the patients were subgrouped into two groups: with/without numbness. According to the research criteria, numbness was considered the clinical correlate of peripheral nerve dysfunction. The percentage of female patients who experienced numbness was significantly higher (*p*-value 0.03) (Fig. 1). The quantitative parameters of the IPA in terms of MA, NT and turns/amplitude ratio did not show any significant differences between the manifesting and the non-manifesting subjects. As well as the SAS showed. Meanwhile, quantitative measures of MAS showed a highly significant difference (*P*-value 0.005) between the two subgroups (Table 1).

It is to be noticed that, out of the 11 patients experiencing numbness, 7(63.63%) patients had abnormal NCS, one (9.1%) had suspected results and three (27.27%) had normal NCS. On the other hand, NCS conducted on 34 patients, that did not experience numbness, revealed 27 (79.41%) subjects with normal

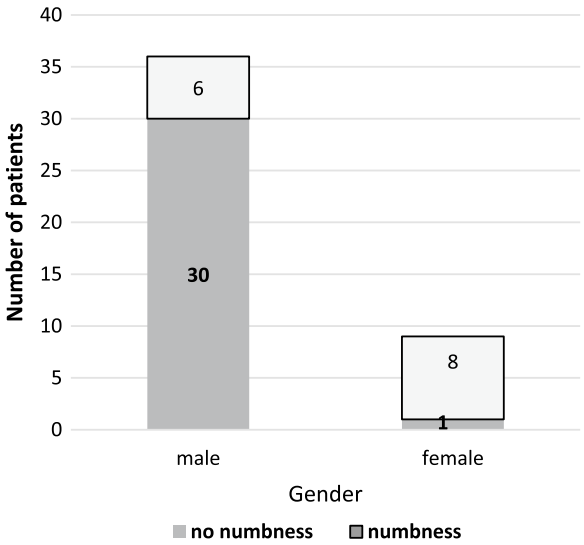

Fig. 1 Gender distribution and clinical presentation of numbness among the studied patients; 80% (36/45) of the recruited patients were males. The percentage of females who experienced numbness was significantly higher (*P*-value = 0.03)

Table 1 Demographic and quantitative parameters in patients who experienced numbness and those who did not

	No numbness (*n* = 34)	Numbness (*n* = 11)	*P*-Value
Age Median (IQR)	53.5 (46–59)	56 (48–58)	0.6
Gender Male	30 (88.24%)	6 (54.54%)	0.03
IPA mean amp (SD)	694.64 (251.53)	669.91 (273.24)	0.8
IPA turns/s Mean (range)	525 (480–639)	621 (374–1444)	0.9
IPA turns-amp-ratio mean (range)	0.74 (0.67–1.2)	0.61 (0.55–4.22)	0.6
SAS (Uln-Sural) Mean (SD)	1.48 (0.58)	1.14 (0.92)	0.1
MAS (Uln-Per)	1.69 (0.52)	1.18 (0.38)	0.005

IPA interference pattern analysis, *SD* standard deviation, *s* second, *amp* amplitude, *SAS* sensory amplitude score, *Uln* ulnar nerve, *MAS* motor amplitude score, *per* peroneal nerve

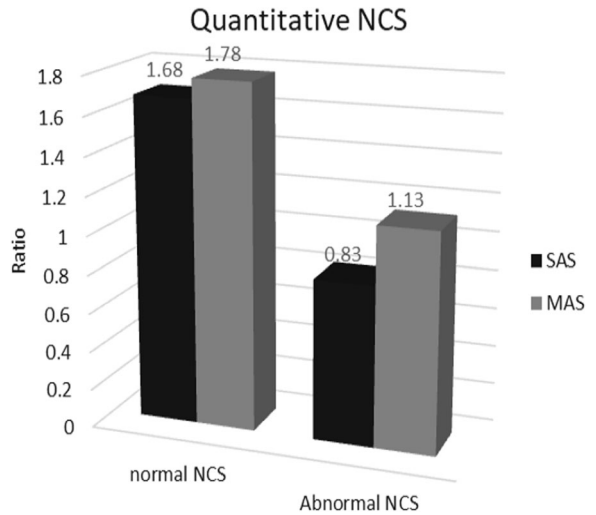

Fig. 2 Sensory amplitude score (SAS) and motor amplitude score (MAS) in patients sub- grouped according to conventional nerve conduction studies. The SAS and the MAS scores were significantly lower in patients with abnormal NCS (*p*-value < 0.0001)

studies, 6 (17.65%) subjects with abnormal studies and only one (2.94%) subject with suspected results.

After subgrouping patients according to NCS into normal NCS 30(66.7%), and abnormal /suspected NCS 15(33.3%), we observed that the complaint of numbness was acknowledged in patients with abnormal/suspected NCS significantly more than those with normal NCS (*P*-value 0.003). Furthermore, the SAS and the MAS mean values were significantly lower in patients with abnormal/suspected NCS than those with normal NCS (*P*-value < 0.0001) (Fig. 2). However, the quantitative parameters of IPA, including MA, NT and turns/amplitude ratio showed no significant differences among the two subgroups. Abnormal NCS were all of axonal pattern (Table 2).

Furthermore, correlative studies were performed between the MAS/SAS and the IPA parameters. There was a positive significant correlation found between the IPA MA and the SAS parameter (*p*-value = 0.04). Meanwhile, the other parameters of IPA did not show any significant correlation with either the SAS or the MAS (Table 3).

Finally, we assessed the diagnostic performance of the MAS and the SAS in detecting abnormal NCS. As for the SAS parameter, the area under the "ROC" curve was 0.88, with a cut-off point ≥ 1.16. It had 80% sensitivity and 73.33% specificity for exclusion of abnormal NCS (Fig. 3).

The area under the "ROC" curve of the MAS parameter was calculated to be 0.86, with a cut-off point ≥ 1.34. It had 80% sensitivity and 80% specificity (Fig. 4).

Table 2 HCV subgroups-depending on their nerve conduction results

	Normal (*n* = 30)	**Abnormal/suspected (*n* = 15)**	***P*-value**
Age Median (IQR)	53 (46–57)	57 (48–60)	0.08
Gender Male	25	11	0.4
Numbness	3 (10%)	8 (53.3%)	0.003
IPA mean amp Mean (SD)	704.86(268.79)	656.73 (228.42)	0.6
IPA turns/s Median (IQR)	537 (486–627)	508 (378–911)	0.45
IPA turns-amp-ratio Median (IQR)	0.74 (0.66–1.2)	0.68 (0.55–2.85)	0.4
SAS(Uln-Sural) Mean (SD)	1.68 (0.61)	0.83 (0.45)	< 0.0001
MAS (Uln-Per) Mean (SD)	1.78 (0.46)	1.13 (0.37)	< 0.0001

IPA interference pattern analysis, *SD* standard deviation, *s* second, *amp* amplitude, *SAS* sensory amplitude score, *Uln* ulnar nerve, *MAS* motor amplitude score, *per* peroneal nerve

Table 3 Correlation between MAS /SAS and IPA parameters

	IPA_mean amp	**IPA_turns/sec**	**IPA_turns/amp ratio**
SAS (Uln-Sural)			
Correlation coefficient	0.31	− 0.1	− 0.12
P-value	0.04	0.7	0.4
MAS (Uln-Per)			
Correlation coefficient	0.15	0.1	0.05
P-value	0.3	0.6	0.5

SAS sensory amplitude score, *MAS* motor amplitude score, *Uln* ulnar nerve, *per* peroneal nerve, *s* second, *amp* amplitude

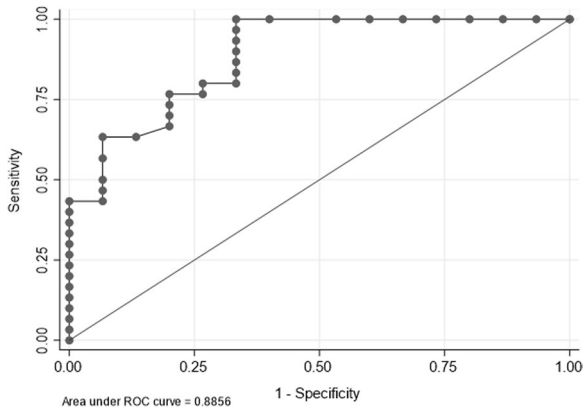

Fig. 3 "ROC" curve for the diagnostic performance of sensory amplitude score (SAS) in detecting abnormal nerve conduction studies (NCS). It had 80% sensitivity and 73.33% specificity for exclusion of abnormal NCS

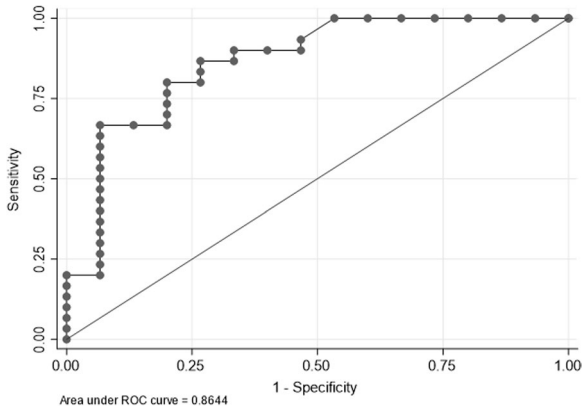

Fig. 4 ROC curve for the diagnostic performance of motor amplitude score (MAS) in detecting abnormal nerve conduction studies (NCS). It had 80% sensitivity and 80% specificity

Discussion

HCV infection is the most common cause of liver cirrhosis in Egypt [18]. The massive national health program that has been launched to eradicate HCV infection in Egypt triggered the aim of this study; to assess neuropathy using different non-conventional methods among HCV patients.

This male predominance was reflected in one way or another on the Child–Pugh classification of the studied patients, most of the patients had Child–Pugh "A" classification (68.9%). This could be explained by higher albumin levels noted in the male patients (mostly hormonal effect) as compared to the females [19]. Moreover, patients with hepatic encephalopathy and severe lower limb edema (due to albumin deficiency) were excluded from this study. Patients with hepatic encephalopathy usually lack co-operation, which was mandatory for the IPA performance. Lower limb edema was an obvious obstacle to eliciting valid NCS responses.

This acknowledged gender discrepancy could be attributed to more than one factor. Occupational exposure (farming for example) had made the males the main target for parenteral anti-bilharzial therapy, which was the main cause of the HCV in Egypt. Furthermore, estrogen and androgen hormones do play a role in immune responses. While estrogen has an immune-stimulating effect, androgen has an immune-suppressing effect. That is why females have stronger humoral and cellular responses to viral infections [20].

The majority of the patients (68.9%) had Child–Pugh "A" classification; this could be explained partially by higher albumin levels found in the male patients compared to female patients (mostly due to hormonal effects) in the study done by Saif-Al-Islam and colleagues in 2020 [19]. Another contributing factor is our willingness to exclude patients with hepatic encephalopathy and severe lower limb edema, which are hindrances to the performance of the IPA (that needs patient co-operation) and eliciting valid NCS responses.

A high prevalence of peripheral neuropathy has been documented in HCV infection which accounts for 40–75%, irrespective of the presence of mixed cryoglobulinemia [21]. This variation comes in accordance with the disease stage, duration, and clinical/electrophysiological protocols for neuropathy ascertainment [22].

A few studies have been carried out in developed countries on HCV-related neurological manifestations. Santoro and colleagues performed a study on Italian HCV patients in 2006, which revealed electrophysiological diagnosis of peripheral neuropathy in 15.3% irrespective of cryoglobulinemia [23]. A more recent study in 2014 by Biasiotta and colleagues applied NCS and laser evoked potentials as well to test for small fiber neuropathy. They estimated peripheral neuropathy to be 68% (45/69) of their HCV patients [24]. Moreover, a retrospective study was done by Feldman and colleagues in 2019 to assess neurological manifestations associated with cryoglobulinemia due to HCV and another cause. Peripheral neuropathy appeared to affect 92% of their patients with definite/possible cryoglobulinemia [25].

Based on the clinical background, numbness is perceived as the presence of dysesthesia or paresthesia. Numbness was reported in our study by only 11 patients (24.44%), with a significant female predominance. Among the 45 studied participants, abnormal NCS had been found in (15/45) patients, accounting for 33.3%, almost half of them (8/15; 53.3%) experienced numbness. Clinical and electrophysiological evidence of neuropathy were found in 17.8% (8/45). Subclinical neuropathy was detected electro-physiologically in 20.6% (7/34) of the patients with no numbness reported.

Our findings agree with the sensory abnormalities detected among the hepatic patients studied by Abdelkader and colleagues 2014 which was about 22%, and other studies conducted on Egyptian patients with a prevalence ranging between 15.6 and 30% [26, 27]. Higher percentages of clinically diagnosed peripheral neuropathy were concluded in studies conducted by Abdel Khalek and colleagues and Cacoub and colleagues, which revealed peripheral neuropathy in 45% and 50% of the studied patients, respectively [28, 29].

Differences in the criteria of patient enrollment together with variable scores and methods used in the clinical diagnosis of peripheral neuropathy may have led to this variation in the literature. Interestingly, not all the patients complaining of numbness had abnormal NCS. Pure small fiber neuropathies which may be presented by

paresthesia/numbness are associated with normal NCS which tests large fibers mainly [30].

The pattern of peripheral neuropathy was axonal in all the studied patients and sensory abnormality was the chief finding. The sensory abnormality predominance is in line with Abdel Khalek and colleagues in 2012 (96.9%), Al kafrawy and colleagues in 2014 (100%) and Mapoure and colleagues in 2018 (96.7%) [27, 28, 31].

To the best of our knowledge, this is the first study to apply quantitative EMG; IPA on HCV patients. By assessing different parameters of the IPA technique in the form of MA, turns/ MA ratio and NT. The IPA technique was recently applied to 22 patients with different neurological disorders by Kobayashi and colleagues in 2020 [32]. Patients with carpal tunnel syndrome, ulnar neuropathy at the elbow, radiculopathy, diabetic neuropathy, and Guillain–Barre syndrome were included to assess the sensitivity of the IPA in terms of activity, NT and MA during maximum voluntary contraction. They concluded that activity, defined as the time with myoelectric signals recorded during one second, had a stronger correlation with the qualitative evaluation grade than other parameters studied.

In our study, none of the above-mentioned parameters show significant differences between patients with normal, versus, abnormal NCS or between patients experiencing numbness and those without. This could be attributed to the low sensitivity of the IPA method as compared to the NCS, which is only 74% [17].

In our study, we used the quantitative nerve conduction parameters; the MAS and the SAS scores, which were launched by Cocito and colleagues in 2010 [15]. Surprisingly, only the MAS score, which is a motor score, differed significantly between patients who reported numbness, which is a sensory complaint, and those who did not report it. The authors are assuming that the clinical occurrence of numbness follows a silent subclinical phase, which might explain this unexpected correlation; more expressed nerve endings affection, leading to clinical symptoms, is more related to the affection of the relatively larger motor fibers caliber, while both showed a significant difference between patients with normal and abnormal NCS.

By further evaluation of the sensitivity of both the MAS and the SAS scores using the "ROC" curves, we have found that the SAS score with values ≤ 1.16 had 80% sensitivity and 73.33% specificity for expecting that the patient would have abnormal NCS. While that for the MAS score, values ≤ 1.34 had 80% sensitivity and 80% specificity for expecting that the patient would have abnormal NCS.

To the best of our knowledge, no other recent studies have applied quantitative scores in the form of MAS or SAS scores. Two studies were performed years earlier that used other quantitative scores such as the study conducted by Papanas and colleagues in 2010 addressing the sensitivity of different parameters in the form of amplitude ratios between different nerves, they concluded the sural sensory amplitude/Radial motor amplitude ratio was the most useful diagnostic indicator for detection of polyneuropathy [33].

Moreover, another hospital-based study that compared the F-wave index (calculated using other F-wave parameters such as persistence, chrono-dispersion, and latency, taking into consideration the limb length) could be considered as a sensitive parameter for the detection of neuropathy; particularly in the upper limbs as compared to the minimum F-wave latency alone [34].

Conclusion

We are concluding that the MAS or the SAS scores could be used as good and easy screening tools for detection of neuropathy by examining just two nerves especially in patients who could not tolerate detailed NCS examination. Yet, we are recommending the expansion of the non-conventional NCSs to other etiologies of polyneuropathy.

Limitations of this study

- Electrophysiological evaluation of small fibers was not performed that could be correlated better to the numbness reported by the patients (electrophysiological tests assessing small fibers were not performed) or tests that address nerve excitability.
- Cryoglobulinemia was not assessed (not of the routine laboratory tests) and accordingly was not correlated to the NCS findings; however, neuropathy was reported in the literature irrespective to the presence of cryoglobulinemia.

Abbreviations

NCS	Conventional motor and sensory conduction studies
EDHS	Egyptian Demographic and Health Surveys
EMG	Electromyography
HCV	Hepatitis "C" virus
IPA	Interference pattern analysis
MA	Mean amplitude
MAS	Motor amplitude score
MCSs	Motor conduction studies
NT	Number of turns
SAS	Sensory amplitude score
SCSs	Sensory conduction studies
SPSS	Statistical Package for the Social Sciences
WHO	World Health Organization

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Author contributions
RG achieved the methodology, shared in writing the manuscript draft. SE plotted the hypothesis, was the research manager, helped in general revision of the manuscript. MB revised the practical and theoretical inputs at each milestone of the research. MK was responsible for the progress of the clinical part of the research, revised relevant theoretical segments in the manuscript. DS organized the results segments, helped in discussion generation, helped in editing the manuscript.

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Availability of data and materials
The data that support the findings of this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
Study had the approval of the Ethics Committee for research of the Faculty of Medicine—Cairo University (MS-88 2019) with clinical trial registration number (NCT04340999). A written informed consent was taken from each patient.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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