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The Validity of Different F Wave Parameters in The Diagnosis of Diabetic Axonal Polyneuropathy

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Abstract

Background The underlying pathology of the vast majority of diabetic polyneuropathies is axonal degeneration. F wave study is one of the most sensitive indices of the severity of neuropathy.

Objective To test the validity of different F wave parameters including F minimum latency, F wave index and F Jitter in the diagnosis of diabetic axonal peripheral neuropathy.

Methods Eighty type 2 diabetics aged 52.57±5.62 years with disease duration of 1 to 18 years and 90 aged-matched healthy volunteers serve as the control group. Both groups were submitted to medical history, clinical neurological examination, and electrophysiological tests of both upper and lower limbs.

Results Tibial and ulnar F wave latencies were significantly prolonged in diabetic patients ($p < 0.001$). Tibial F index for male patients shows significantly lower value as compared to the control group. Ulnar F wave latency was 76.7% sensitive and 89.3% specific in female patients while tibial F wave latency was 80% sensitive and 81.3% specific in male patients.

Conclusion F wave is a precise parameter in detecting diabetic axonal peripheral neuropathy. Minimal F-wave latency is more sensitive than both F index and F Jitter in the diagnosis of axonal neuropathy in diabetic patients.

Keywords DM, Axonal neuropathy, Ulnar, Tibial, F-wave latency, F-jitter, F-index

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List of abbreviations: NCS = Nerve conduction study, ROC = Receiver operating characteristic

Introduction

Diabetic neuropathies are frequent chronic complications of diabetes mellitus [(1)]. Chronic distal symmetric polyneuropathy is the most common type and accounts for 75% of cases of diabetic neuropathies [(1,2)].

The diagnosis of diabetic polyneuropathy depends on the appropriate clinical history and clinical neurological examination [(3)]. According to the Toronto consensus criteria, probable neuropathy is defined as the presence of at least two of the following: neuropathic symptoms, reduced distal sensation, or diminished or absent ankle reflexes. Abnormal nerve conduction study (NCS) or a proven study of small-fiber function [(4)] would confirm the final diagnosis.

For an accurate diagnosis of diabetic sensorimotor neuropathy, studies always recommend the presence of a combination of neuropathic symptoms and signs plus certain and specific abnormalities in NCS criteria [(5)]. On many occasions, the diagnostic value of NCS is

questioned, i.e., patients presented with signs of atypical neuropathy may need an electrodiagnostic examination to diagnose his condition. On the reverse, patients with typical diabetic polyneuropathy may not need NCS to settle the diagnosis [6].

Seventy years have been passed since Magladery and McDougal [7] describes the importance of F-wave in the assessment of peripheral neuropathies, in particular, those of axonal type [8]. It serves as a sensitive measure for axonal polyneuropathy and radiculopathy and is used in the diagnosis of diabetic polyneuropathy, Guillain–Barrè syndrome, and amyotrophic lateral sclerosis. F waves also help in the early detection of abnormality in motor fibers [9].

Peripheral neuropathies can be documented by F-wave abnormalities even before any change in the compound muscle and sensory nerve action potentials and might be the only abnormality disclosing a neuropathy, precisely the diabetic type [10]. F wave slowing to a lesser degree may be seen in other axonal and mixed polyneuropathies [11] though, F wave latency slowing seems to be of value in nerve pathologies especially in patients with diabetes mellitus [12].

Various F wave parameters are used for the diagnostic evaluation of peripheral nerve disorder; among them are the minimal F wave latency, F wave chronodispersion, F wave persistence, and the F wave conduction velocity [11,13-16].

The objective of current study is to test the validity of different F wave parameters including F minimum latency, F wave index and F Jitter in the diagnosis of diabetic axonal peripheral neuropathy.

Methods

This is a case-control study carried out at the Neurophysiology Department of Al- Imamein Al-Kadhimein Medical City in Baghdad, for the period from Dec. 2017 to Jul. 2018.

The study was approved by the Iraqi Council of Medical Specialization (Decision number: 860, Date 12.02.2018). Written informed consent was obtained from all individual participants included in the study.

Subjects

Eighty type 2 diabetic patients (40 females and 40 males) with clinical signs and symptoms of peripheral neuropathy were recruited for the study. Their ages range from 40 to 60 years (mean±SD = 52.57±5.62 years) with a disease duration of 1-18 years. Another 90 aged-matched healthy volunteers (43 females and 47 males) with a mean age of 51.93±6.66 years served as the control group.

Exclusion criteria

Those patients who had a history of carpal tunnel syndrome, Guillian-Barre syndrome, ulnar and tibial neuropathy, myopathy, hypothyroidism, neuromuscular disorders, fractures of upper or lower limbs, and patients with pacemaker were excluded from the study.

Methods

History and clinical examination

The patients were referred by senior Neurologist and/or Endocrinologist after taking brief medical history from each patient including age, onset, and duration of symptoms, past medical history, and signs and symptoms of peripheral neuropathy based on the Toronto Clinical Score [17] (which included the presence of clinical features such as unpleasant, unusual or abnormal sensation such as burning pain, electric shock-like sensations, tingling, pins and needles formication, prickly feeling and cramp-like sensation in the lower and upper limb).

Also, a clinical neurological examination was done for each patient, including motor, sensory and cranial nerve examination. Deep tendon reflexes were graded based on the amplitude of the response [18] and muscle strength (power) grading was measured according to the extended MRC scale [19].

Electrophysiological assessments

Key point (Medtronic functional Diagnosis A\S - DK-2740 Skovlunde, Denmark) EMG machine

was used throughout the study. The room temperature was monitored between (25-28 °C) during the test procedures and skin temperature between (32-34 °C) was ensured using a skin thermometer.

According to the methods adopted by Preston and Shapiro [20], The following electrophysiological tests were performed:

1. Bilateral sensory nerve conduction (SNC) of the median, ulnar, and sural nerves.
2. Bilateral motor nerve conduction (MNC) of the median, ulnar, common peroneal and tibial nerves recorded from abductor digiti minimi, abductor pollicis brevis, extensor digitorum brevis, and abductor hallucis brevis, respectively.
3. Bilateral F wave elicited by distal stimulation of the ulnar and tibial nerves at the wrist or ankle and recording from abductor digiti minimi and abductor hallucis brevis at relaxed state, respectively.

A total of 10 stimuli were considered appropriate to explore the full potential of F waves. To be clearly identifiable, F waves should be at least 20 µV in peak-to-peak amplitude to differentiate them from background noise. The conventional stimulus intensity is 25 percent above maximal for eliciting a direct response. This provides a consistent physiologic environment for eliciting F waves.

The following F wave parameters were studied:

a) F wave minimum latency which represents conduction of the largest and fastest motor fibers and measured from the start of the stimuli to the onset of the response.
b) F persistence which is a measure of the number of F waves obtained for the number of stimulations.
c) F choronodispersion which denotes the degree of scatter among consecutive F waves and is determined by the difference between the minimal and maximal F wave latencies. It indicates the range of motor conduction velocities between the smallest and largest myelinated motor axon in the nerve.
d) F index: calculated by the following equation: F wave index = [F persistence × Arm length) / (F latency × F chronodispersion] [21].
e) F jitter: stands for the latencies of consequent F waves. If a specifically recorded trace showed and absent F wave, it will be omitted and the next trace was analyzed instead. F jitter = (|f2 – f1| + |f3 – f2|+ |f4 – f3)…. / (n – 1) [22].

An obstetric tape measure was used for limb length. In the upper limbs, the surface measurement from the stimulus point to the C7 spinous process with the limb extended and abducted 90 degrees pronated via the axilla and midclavicular point gives a close estimate of the nerve length. For the lower limb, the nerve course is measured from the stimulus site to the T12 spinous process by way of the knee and greater trochanter of the femur.

The electrophysiologic settings for adequate display of F waves were an amplifier gain of 200 or 500 µV per division and a sweep of 5 or 10 msec per division.

Statistical analysis

Microsoft excel 2016 and SPSS (statistical package for social sciences) version 23 were used as a software to do the statistics. Continuous data were presented as mean±standard deviation, and comparison between means of study groups was done by using unpaired student t-test. A p-value of less than 0.05 was considered significant. Cutoff values of the prolonged F minimum latency, F jitter, and decreasing F index and accordingly the sensitivity and specificity were evaluated by using the receiver operating characteristic (ROC) curve.

Results

Table 1 shows the demographic and neurophysiologic data of the diabetic patients. The impact of gender differences in limb length reflected as significant difference between females and males considering the upper and lower limbs ($p = 0.007$; $p < 0.001$). No significant difference was noticed between the age of the patients 52.57±5.62 years and control subjects 51.93±6.66 ($p = 0.692$).

No significant difference was noticed in the mean values of ulnar and tibial F latency, F index and F jitter between the right and left side in both genders of the control and patient groups (Table 2).

Table 1. Demographic and neurophysiologic data of diabetic patients

Age (years)		52.57±5.62
Sex	Females	40
	Males	40
HbA1c %		8.99±2.31 (6.5-13.5)
Disease duration (years)		1-18
Limb length (cm)		
Females	Upper limb (female)	72.94±4.7
	Lower limb (female)	86.35±3.87
Males	Upper limb (male)	78.03±4.35
	Lower limb (male)	92.1±3.29
Compound muscle action potential amplitude (mV)	Median	4.2±1.3
	Ulnar	6.04±1.2
	Peroneal	2.42±0.6
	Tibial	3.8±1.22
Sensory nerve action potential amplitude (µV)	Median	14.31±1.7
	Ulnar	12.21±1.7
	Sural	5.62±3.1
Motor conduction velocity (m/sec)	Median	53.73±3.7
	Ulnar	51.12±2.3
	Peroneal	42.6±2.7
	Tibial	45.2±2.2
Sensory conduction velocity (m/sec)	Sural	42.35±2.4
	Median	53.61±3.8
	Ulnar	52.3±2.7

CMAP = compound muscle action potential; SNAP = sensory nerve action potential; MCV = motor conduction velocity; SCV = sensory conduction velocity.

Accordingly, these data were pooled together and tabulated as one group for females and males for future comparisons. Table 3 illustrates longer tibial and ulnar F latency ($p < 0.001$) in female patients as compared to the control group. Also, the tibial F index was significantly lower ($p = 0.038$) in female patients when compared to female controls.

For males, significantly longer tibial and ulnar F latency in the patient group when compared to the control group ($p < 0.001$). likewise, the tibial and ulnar F index was significantly reduced ($p < 0.001$; $p = 0.001$, respectively) in male patients as compared to male controls.

Sensitivity and specificity of F wave parameters

A ROC analysis curve was constructed for F minimum latency, F index, and F jitter for the tibial and ulnar nerves in both genders. Regarding female patients, tibial F latency was 73.3% sensitive and 82.1% specific which is the highest estimated value among other parameters. For the ulnar nerve, the F latency was 76.7% specific and 89.3% specific which was the highest estimated value.

For male patients, tibial F latency has the highest sensitivity (80%) and specificity (84.4%) among the three F wave parameters. Also, ulnar F latency demonstrates 80% sensitivity and 81.3% specificity which is the highest among other parameters (Table 4, Figures 1 and 2).

Table 2. Ulnar and tibial F latency, F index and F jitter in the diabetic patients and controls (unpaired t-test)

Nerve/parameter		Female controls		P-value	Female patients		P-value
		Right side N=43	Left side N=43		Right side N=40	Left side N=40	
Tibial	F latency	47.43±4.02	48.41±3.92	0.520	53.82±5.51	53.74±5.19	0.968
	F index	62.14±23.26	67.14±23.35	0.575	55.33±38.52	43.33±20.59	0.296
	F jitter	0.28±0.2	0.18±0.14	0.128	0.27±0.21	0.38±0.53	0.468
Ulnar	F latency	24.89±1.41	24.98±1.13	0.849	27.13±1.98	26.98±1.9	0.830
	F index	102.86±32.45	132.14±63.39	0.136	95.33±43.89	100.67±39.18	0.728
	F jitter	0.19±0.15	0.2±0.14	0.771	0.19±0.09	0.17±0.13	0.569
Nerve/parameter		Males controls		P-value	Male patients		P-value
		Right side N=47	Left side N=47		Right side N=40	Left side N=40	
Tibial	F latency	50.36±4.31	50.52±4.6	0.919	60.15±9.21	59.08±8.33	0.740
	F index	61.25±19.96	69.38±36.05	0.436	35.33±25.03	39.33±27.64	0.681
	F jitter	0.32±0.26	0.33±0.15	0.888	0.28±0.19	0.3±0.18	0.837
Ulnar	F latency	26.63±2.16	26.96±1.96	0.653	31.03±3.96	30.73±4.3	0.847
	F index	118.75±79.32	131.25±71.45	0.643	80.67±44.15	66.67±29.92	0.318
	F jitter	0.27±0.14	0.21±0.14	0.238	0.21±0.27	0.5±0.94	0.267

N = number of subjects

Table 3. Ulnar and tibial F latency, F index and F jitter of the patients and controls (unpaired t-test)

Nerve/parameter		Females		P-value	Males		P-value
		Control N=86	Patients N=80		Control N=94	Patients N=80	
Tibial	F latency	47.92±3.93	53.78±5.26	<0.001	50.44±4.39	59.62±8.65	<0.001
	F index	64.64±23.01	49.33±30.95	0.038	65.31±28.96	37.33±25.99	<0.001
	F jitter	0.23±0.18	0.32±0.4	0.245	0.32±0.21	0.29±0.18	0.491
Ulnar	F latency	27.06±1.9	24.93±1.25	<0.001	26.79±2.04	30.88±4.06	<0.001
	F index	98±40.97	117.5±51.61	0.115	125±74.53	73.67±37.74	0.001
	F jitter	0.18±0.11	0.2±0.15	0.643	0.24±0.14	0.36±0.69	0.355

N = represent the number of limbs examined (right and left)

Table 4. The area under the curve, sensitivity, specificity, and cutoff value for tibial and ulnar F wave parameters in patients of both genders

Nerve/parameter		AUC	Sensitivity	Specificity	Cutoff value
Females					
Tibial	F latency	0.828	73.3%	82.1%	52.05
	F index	0.693	46.4%	73.3%	65.0
	F jitter	0.562	50.0%	50.0%	0.24
Ulnar	F latency	0.827	76.7%	89.3%	26.35
	F index	0.610	46.4%	66.7%	0.105
	F jitter	0.510	50.0%	56.7%	0.195
Males					
Tibial	F latency	0.850	80.0%	84.4%	54.55
	F index	0.808	68.8%	73.3%	45.0
	F jitter	0.538	50.0%	56.7%	0.315
Ulnar	F latency	0.832	80.0%	81.3%	28.65
	F index	0.768	65.6%	70.0%	85.0
	F jitter	0.549	59.4%	63.3%	0.205

AUC = area under the curve

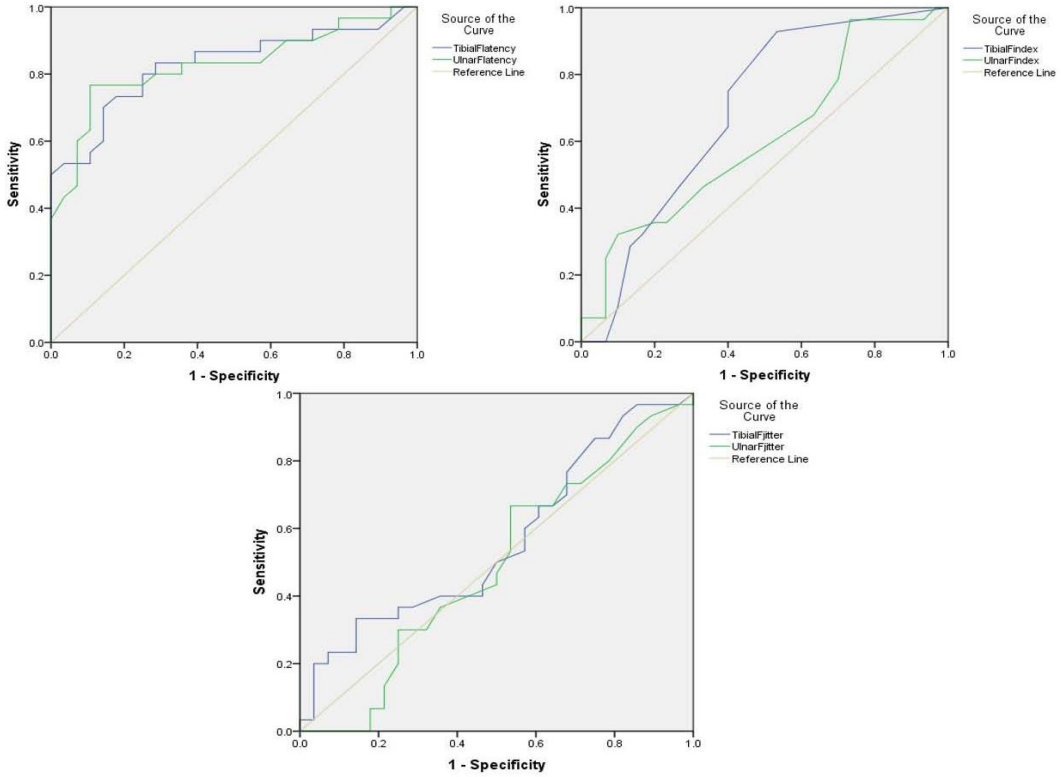

Figure 1. Receiver operating characteristics curve for tibial and ulnar. (upper left) F latency (upper right) F index in male patients (bottom) F jitter in female patients

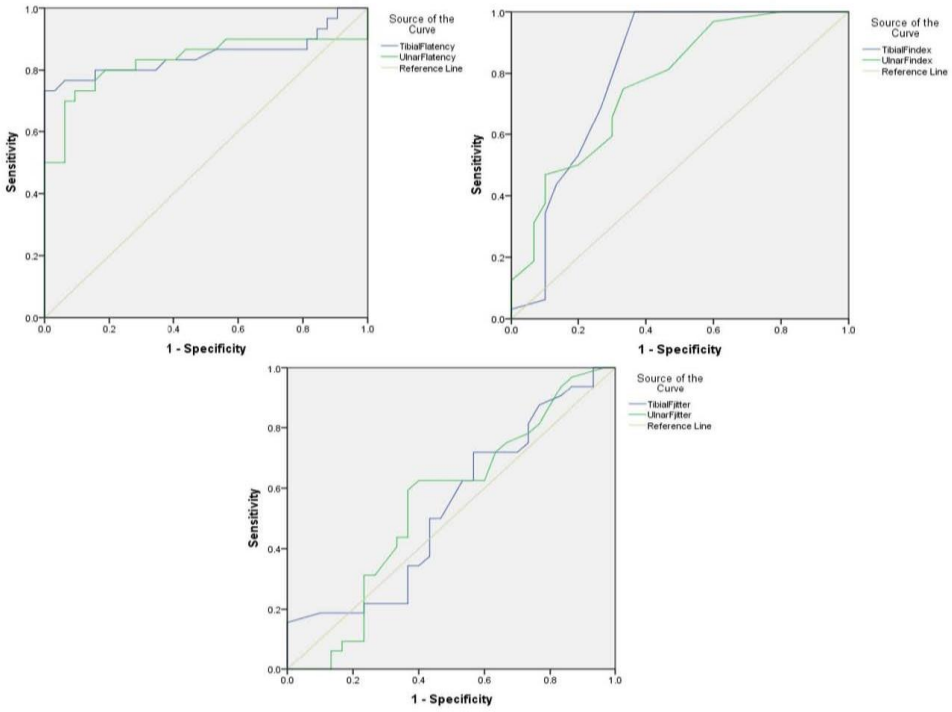

Figure 2. Receiver operating characteristics curve for tibial and ulnar. (upper left) F latency (upper right) F index in male patients (bottom) F jitter in male patients

Discussion

In peripheral neuropathies, F-wave minimal latency is usually prolonged and it could be abnormal in cases where the motor conduction studies are normal [23]. Moreover, it is also crucial in axonal neuropathies when compared to conventional motor conduction studies [24]. Furthermore, it was the most stable and consistent parameter for serial NCS in the same subjects [23] and is the reliable measurement in patients with diabetic neuropathies [16].

Previously, during routine electrophysiological studies of patients with diabetes mellitus, F wave has been studied to assess the proximal parts of the motor nerves with almost conflicting outcomes. As some researchers did not notice any differences between the proximal and distal nerve segments, others have revealed slightly but significantly more distinct slowing in the distal nerve segments [11].

Because the minimal F wave latency is a direct estimate of the conduction along the entire length of the nerve, it can correlate with height or limb length. Therefore, it is more reliable and can amplify nerve conduction in detecting peripheral neuropathies than using the conventional compound muscle action potential method, which is limited to a small segment of a peripheral nerve.

The recorded F-wave minimum latencies of ulnar and tibial nerves were per that reported by other researchers [25,26]. No significant side to side difference was demonstrated in the F-wave minimum latency of upper and lower extremities. This was also reported by others [27,28] but contrary to the results of other researchers [29] who reported intrasubject variability in F-minimum latency of upper and lower limb nerves. The latter discrepancy could be due to the difference in the subjects' age studied.

The present study has verified the direct relationship between minimum F wave latency and height for all nerves as documented by others. The taller the subject, the longer the nerve, and hence, the latency of conduction also prolongs. F wave latency has been documented to prolonged with height by 0.2 ms/cm in the upper and 0.4 ms/cm in the

lower limbs [30,31]. The present data confirm in apart the well-known correlation of F wave latencies to the limb length and height.

In the present study, a significant effect of limb length on all tested F wave parameters was found; since they all depend on the distance from which the impulse traveled antidromically from the site of stimulation and up to the spinal cord and then descend again. Distance effect on different F wave measurements is demonstrated as follows:

1. F wave minimum latency calculated as the time needed for the impulse to travel up reaching to proximal spinal cord segment and then descend again.
2. F wave jitter corresponds to latencies of consequent F waves [22].
3. F index calculation includes the limb length as one of its factors (F wave index [F persistence × arm length) / (F latency × F chronodispersion] [21].

A significant difference between males and females concerning their limb length (leg and arm length), they were dealt with as two separate groups. Gender had a significant effect on F minimum latency [32]. The effect of gender on nerve conduction parameters can be explained based on gender-wise differences in anatomical and physiological factors [33]. This gender difference in NC parameters could be due to the difference in height as the action potential through the nerve has to travel greater distance [34].

Prolonged F-wave latency was demonstrated in diabetic patients of the current study as compared to the control subjects. This finding was also noticed by other researchers [35]. Moreover, Pan et al. denote that F- waves of the tibial nerves are the most sensitive measure to detect subclinical or overt diabetics [10].

Two factors could contribute to the prolonged F-wave minimal latency; first is the diminished excitability of the anterior horn cells and second is the selective loss of the fastest conducting axons [14].

The present study demonstrates a reduced F index in diabetic patients with peripheral neuropathy as compared to the control subjects. This finding was also reported by Sathya et al [21].

About F- jitter, the results of the current study were contradictory insignificant. In female patients, it shows increment in the tibial nerve and decrement in the ulnar nerve and almost the reverse in male patients. This finding was in contradiction to that of Uludağ et al. [22] which denotes significant increment in F jitter in patients with polyneuropathy. This discrepancy could be attributed to the smaller sample size in their study and type of polyneuropathy (as they did not recognize the peripheral neuropathy whether axonal or demyelinating).

In the present study, F minimum latency shows the highest sensitivity and specificity as compared to the F index and F jitter in the patient group. These findings were in disagreement with the results of Sathya et al. [21] considering F index and Uludağ et al. [22] considering F jitter. This discrepancy could be ascribed to the difference in height and limb length, smaller sample size and type of neuropathy.

The F minimal latency was the parameter used most frequently and of which sensitivity is highest in demyelinating polyneuropathy [9]. This study confirms that F-wave minimal latencies can detect early changes in predominantly axonal neuropathy. Adding F-wave latencies to the motor and sensory conductions improved the sensitivity of the detection of electrophysiologic abnormalities from 3% to 36% in asymptomatic patients of diabetes [10].

This study concluded that F wave is a sensitive parameter in detecting diabetic axonal peripheral neuropathy, minimal F-wave latency is more sensitive than both F index and F Jitter in the diagnosis of diabetic axonal neuropathy, and measurement of F wave latency highly correlated with the length of the studied nerve. The authors recommend a study with larger sample size, study twenty F wave responses rather than 10 as in this study to increase the chance of detecting any possible changes in F wave and any alteration of motoneuronal excitability, and study the F repeater to assess the available motor neurons with each firing.

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Author contribution
All the authors have directly participated in the preparation of this manuscript and have approved the final version submitted. Dr. Yaqoub contributed to the collection of cases and drafted the manuscript. Dr. Kaddori and Dr. Hamdan conceived the study and participated in its design and interpretation. Dr. Kaddori and Dr. Hamdan supported manuscript drafting. All the authors have read and approved the final manuscript.

Conflict of interest
The authors declare no conflict of interest.

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