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ORGINAL ARTICLE

Neurological Manifestation among Patients with Visceral Leishmaniasis at the Tropical Teaching Hospital – Khartoum

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ABSTRACT

Background: Leishmaniasis is an endemic disease in Sudan that caused by Leishmania spp. Several studies suggest neurological manifestations in visceral leishmaniasis, such as burning sensation, and weakness. This study was aimed to assess the frequency of the neurological manifestations in Visceral Leishmaniasis. **Methods:** This is a descriptive, prospective cohort study, was conducted in The Tropical Teaching Hospital – Khartoum for one-year duration. A pretested questionnaire contained the study variables were conducted, nerve conduction Study (NCS) and laboratory tests were done. SPSS v 26.0 was used to analyze the data. **Results:** Forty four percent of total patients (22/50) were symptomatic.Peripheral neuropathy was elicited in 60% (30/50), Numbness has been the most common feature 56.6% (17/30), and Weakness 26.6% (8/30) all were Axonal damage. Sensorimotor neuropathy was exhibited in 70% (21/30), pure motor neuropathy in 26.7% (8/30). Polyneuropathy was encountered in 46.6% (14/30), poly-radiculopathy in 20% (6/30) along with 23.3% (7/30) as mononeuropathy.

Conclusions: peripheral neuropathy was developed in patients with visceral leishmaniasis, frequent occurrence of subclinical neurological manifestations is higher than reported.

Keywords: Visceral leishmaniasis; Peripheral neuropathy; Sensorimotor neuropathy

INTRODUCTION

Leishmaniasis refers to the wide range of clinical diseases produced by *Leishmania Species*, which are world widespread as endemic disease except Australia and Antarctica. In humans and other mammals, Leishmania parasites exist as intracellular amastigote forms within mononuclear phagocytes [1]. The parasite is transmitted in its extracellular promastigote form by phlebotomine sand flies. In many areas, leishmaniasis is a zoonotic disease, in which wild domestic animals or humans are reservoir, but this depends on geographic location [2].

In endemic regions more than 300 million people are at risk of infection [3]. The occurrence of cutaneous leishmaniasis is reported to be one million to one and a half million cases a year, and the incidence of visceral leishmaniasis to be 500,000 cases per year. Visceral leishmaniasis (VL) is endemic in eastern India and Bangladesh, the Sudan, where a major epidemic has occurred over the past

decade among refugees, and in Latin American countries [4].

The clinical manifestations of leishmaniasis depend on the parasite's pathogenicity, which differs in species, and the genetically determined cell-mediated immune response of its human host. Many leishmania infections are asymptomatic and self-resolving. Some are limited to the skin, resulting in cutaneous leishmaniasis, or they affect the mucosa of the nose, mouse, or oral pharynx, resulting in mucosal leishmaniasis. In Visceral Leishmaniasis, the parasite disseminates throughout the reticuloendothelial system [5].

Visceral leishmaniasis usually is underreported with delay in diagnosis and treatment, therefore possible diagnosis of visceral leishmaniasis is based the classic clinical presentation of irregular fever, enlargement of spleen and liver, and abnormal hematological findings in the endemic areas. Patients such as traveler or immigrant to non-endemic countries usually presents with an unusual manner, or in HIV patients might delay the diagnosis [6, 7]. The diagnosis was confirmed by the identification of amastigotes in tissue or by growing promastigotes in culture. Splenic aspiration results in a diagnosis in 96% to 98% of cases [8].

Visceral disease, the most serious and fatal type of leishmaniasis, it was seen in patients with darkening of the skin, and therefore it known as kala-azar or black fever disease [9].

This condition results from systemic infection of the liver, spleen, and bone marrow. Patients presented with wide scale of illness varied from asymptomatic infection or self-resolving disease to severe, life-threatening infection; many cases occur and go unknown for each clinically known case.

The disease characterized by continuous or remittent fever which becomes intermittent at a later stage, weight loss, hepatosplenomegaly, pancytopenia, and hypergammaglobulinemia.

Patients may also be presented with night sweats, weakness, diarrhea, malaise, and anorexia. Melanocyte stimulation causes characteristic skin hyperpigmentation [10].

Visceral Leishmaniasis is not typically associated with neurologic symptoms. But there are rich studies that support the clinical manifestations of neurological effects of leishmaniasis in animal models and human case studies, which indicate that both central nervous system and ocular manifestations are common and sometimes unreported. In this study we aimed to assess the frequency of the neurological manifestations in Visceral Leishmaniasis.

METHODS

The study design was a descriptive, prospective cohort hospital-based study design that was conducted from January 2021 to December 2021 at Omdurman Tropical Teaching Hospital in Omdurman city. It is recognized as the national Centre for tropical diseases in Sudan.

The study included all patients diagnosed with Visceral leishmaniasis in the out-patient clinic and in-patient in Omdurman Tropical Teaching Hospital. Patients that were previously diagnosed with Neurological disease not related to Leishmaniasis or HIV were excluded. The sample size of the study was estimated on total coverage during study period. A total of 50 patients were assigned as study samples.

A pretested administered questionnaire was taken by the Principal Investigator. The questionnaire contains the demographics of the study population and study variables. Laboratory tests were collected from the patients included Complete blood count(CBC), Random blood sugar (RBS), Renal function tests (RFT) with electrolytes, Erythrocyte sedimentation rate (ESR), Thyroid function test (TFT), Serum B12 level, Liver function tests (LFT), and nerve conduction Study (NCS), provided free of charge for all participants). Patients were further investigated according to their neurological presentations using MRI, EMG or CSF analysis.

Ethical consideration:

The local ethics committee (EDC/SMSB) approved the study protocol. All participant's consent was taken through written informed consent in this medical research

Statistical Analysis:

Statistical analysis was performed using the statistical packages of the social science (SPPS). A P value less than 0.05 was considered statistically significant.

RESULTS

In this study the mean age was 26.8 years (± 7.80), most of the participants were males 90%

(45) and females were 10% (5) with M: F ratio 9:1.

The residency of the patients according to Sudanese states was from Gedarif 18 (36%), 11 (22%) in Darfur, five (10%) in Sinnar and Kordufan, two (4%) in White Nile, one (2%) lives in Blue Nile and Khartoum. Seven cases (14%) were reported from Chad.

Fifty-Sex percent (28/50) of the patients were asymptomatic, 44% (22/50) exhibited neurological symptoms, 34% (17 /50) had numbness, 16% (8/50) had weakness, 2% (1/50) had unsteadiness and tremor (Figure 1) noted that some patients have reported more than one symptom, therefore, the total more than the expected. Weakness in the lower limbs in total of 8 patients; was elicited in 87.5% (7/8) and 12.5% (1/8) in both upper and lower limbs. Lower limbs numbness in total of 17 patients; was noticed in 94.1% (16/17), and only 5.9% (1/17) in both upper and lower limbs (Table 1).

Eighteen percent (9/50) of leishmania patients were presented with LMNL signs in their lower limbs, 2% (1/50) presented with LMNL in their upper limbs, ataxic gait, nystagmus, intension tremor and hypoesthesia.

Visceral leishmaniasis was diagnosed mainly based on bone marrow biopsy in 54% (27/50), 28% (14/50) using rK39, 12% (6/50) by lymph node biopsy, 4% (2/50) by DAT, and only 2% (1/50) clinically based (Figure 2).

In symptomatic patients, neurological symptoms emerged in 54.5% (12/22) before starting the treatment, while in 45.5% (10/22) after receiving the visceral leishmaniasis treatment with (P value = 0.8312). Regression of neurological features three weeks after completion of VL treatment were observed in 13.6% (3/22), while 86.4% (19/22) did not showed any improvement.

Nausea and vomiting were reported in 6% (3/50), 4% (2/50) had diarrhea, and the rest had abdominal cramps, headache, myalgia, proximal muscle weakness, 2% (1/50).

Normocytic anemia was found in 60% (30/50) and microcystic anemia in 36% (18/50).Erythrocyte sedimentation rate (ESR) was elevated in 82% (42/50). Impaired liver function tests were observed in 4% (2/50), while ~~S~~erum B12, Thyroid function test, Renal function test, random blood glucose and MRI brain were normal in all patients (Table 2).

Sixty percent (30/50) of patients who underwent nerve conduction study (NCS) exhibited abnormal test and 40% (20/50) were normal. All were axonal nerve damage (30/100%). Peripheral neuropathy was found in 60% (30/50), and 2% (1/50) was diagnosed with cerebellar ataxia (Figure 3).

Among patients with peripheral neuropathy 46.6% (14/30) had polyneuropathy, 23.33% (7/30) had mononeuropathy. 20% (6/30) were poly-radiculoneuropathy, and 10% (3/30) were radiculoneuropathy (Figure 4).

Ulnar nerve was affected in 71.5% (5/7) and only 28% (2/7) affect the peroneal nerve as a part of mononeuropathy. Sensorimotor neuropathies were encountered in 70 % (21/30), 26.7% (8/30) were pure motor neuropathies, and only 3.3% (1/30) was pure sensory neuropathy (Figure 5).

The association between the presence of neurological symptoms and nerve conduction study was found to be statistically significant with a P value 0.001.

Table 1: The duration, site, and neurological symptoms of developing visceral leishmaniasis in Sudanese patients

Duration ~~of developing Visceral leishmaniasis~~		**Frequency % (N=50)**
1-6 months		**96% (48/50)**
7-12 months		**4% (2/50)**
Site of the neurological symptom	**Weakness Frequency (%)**	**Numbness Frequency (%)**
Lower Limbs	**87.5% (7/8)**	**94.1% (16/17)**
Upper & Lower Limbs	**12.5% (1/8)**	**5.9% (1/17)**
Total	**100% (8/8)**	**100% (17/17)**

Table 2: Laboratory and radiological findings in patients with visceral leishmaniasis (Total 50)

Investigation's findings		Frequency (%)
Complete blood count	Normocytic anemia	30/50 (60%)
	Microcytic anemia	18/50 (36%)
Serum B12 Level	Normal	50/50 (100%)
Thyroid function test	Normal	50/50 (100%)
ESR	High	41/50 (82%)
Liver function tests	Abnormal	2/50 (4%)
Renal function tests	Normal	50/50 (100%)
Random blood sugar	Normal	50/50 (100%)
MRI brain	Normal	1/50 (2%)

Table 3: **Frequency of peripheral neuropathy in affected limb and side patients with Visceral Leishmaniasis (Total 50 patients)**

Affected limb	Frequency (%)
Upper limbs	5/50 (10%)
Lower limbs	30/50 (60%)
Upper & Lower limbs	5/50 (10%)
Affected Side	
Right side	4/50 (8%)
Left side	2/50 (4%)
Both sides	25/50 (50%)

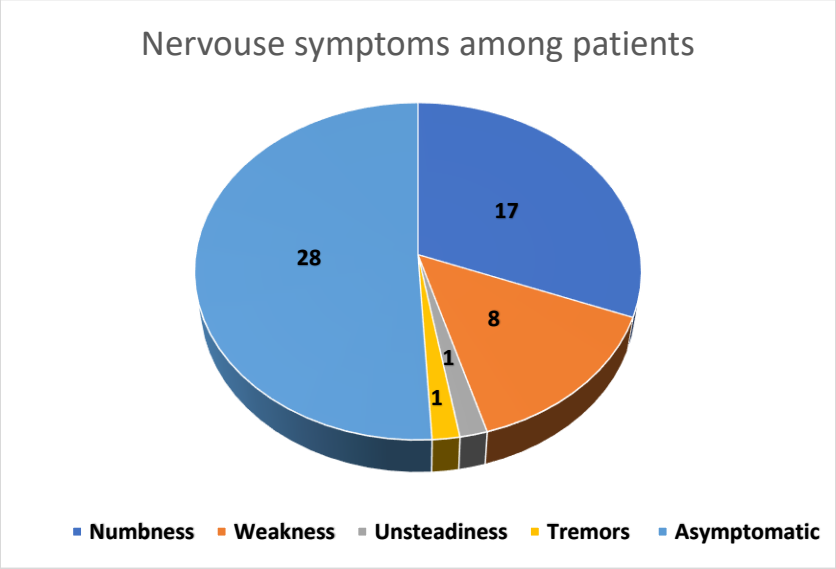

Figure 1: The neurological symptoms developed in (50) patients with visceral Leishmaniasis. *Note: some study participants may have reported more than one symptom. Therefore, the total may be more than the expected.*

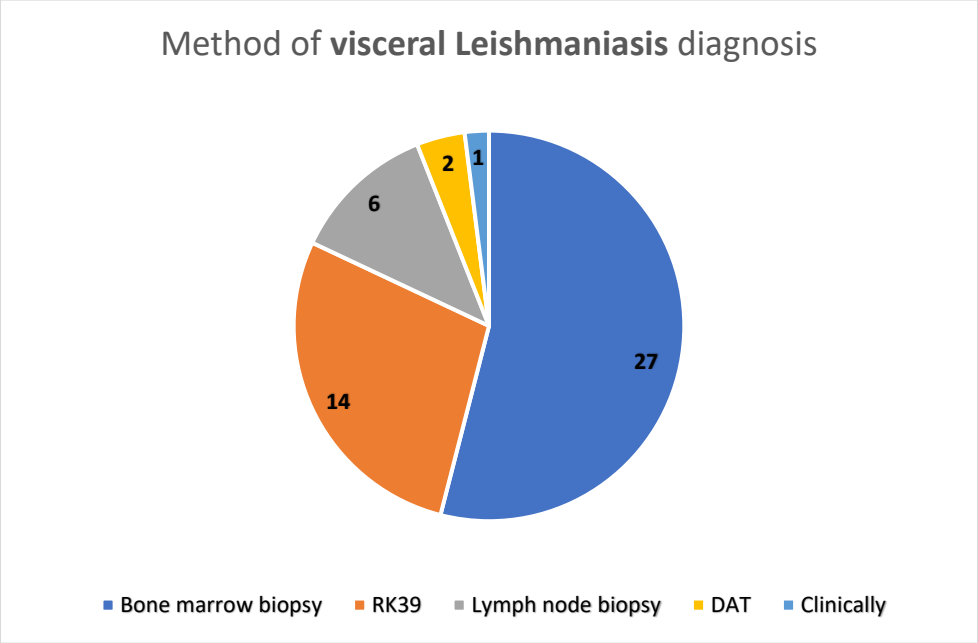

Figure 2: The method of diagnosis of visceral Leishmaniasis in (50) patients

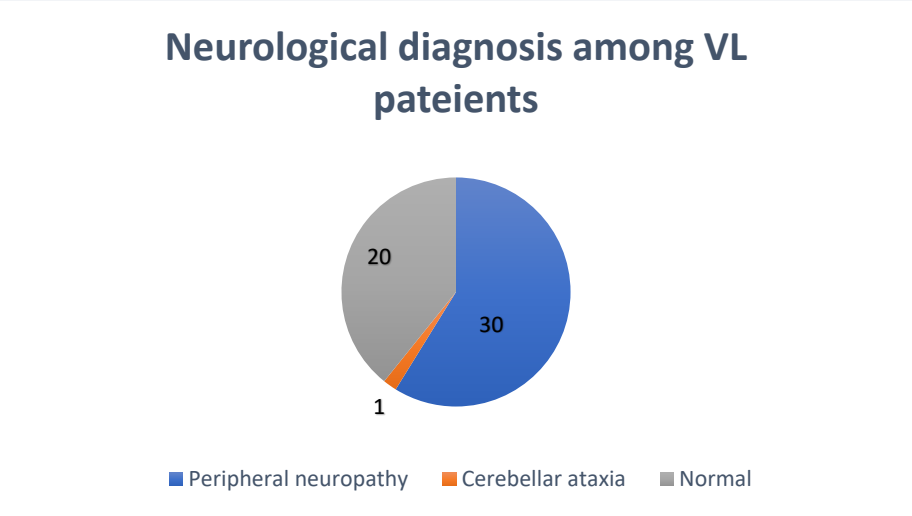

Figure 3: Neurological diagnosis in (50) patients with visceral leishmaniasis.

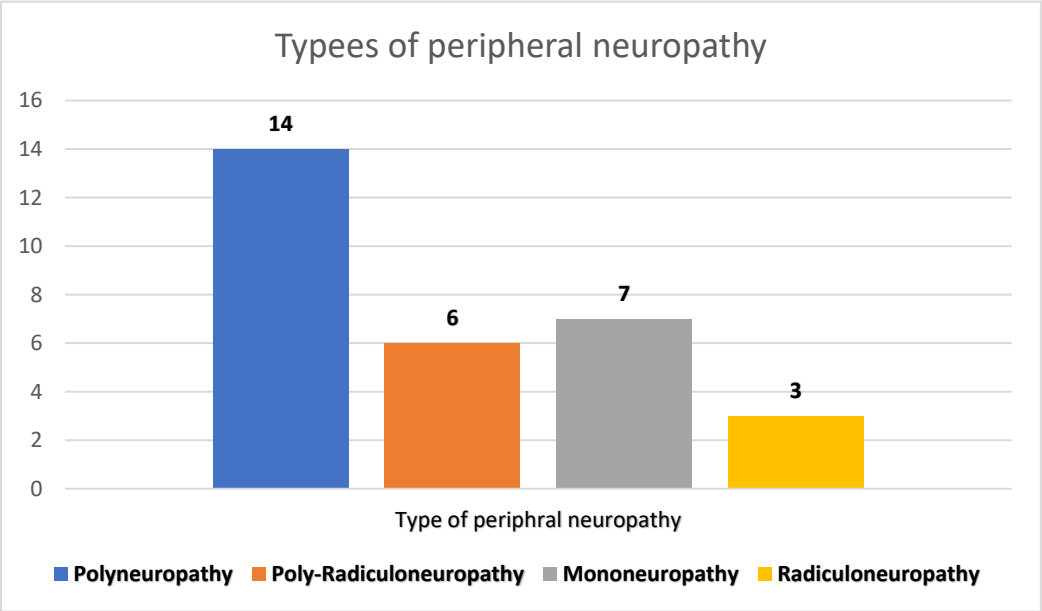

Figure 4: Type of peripheral neuropathy in (30) patients with visceral leishmaniasis.

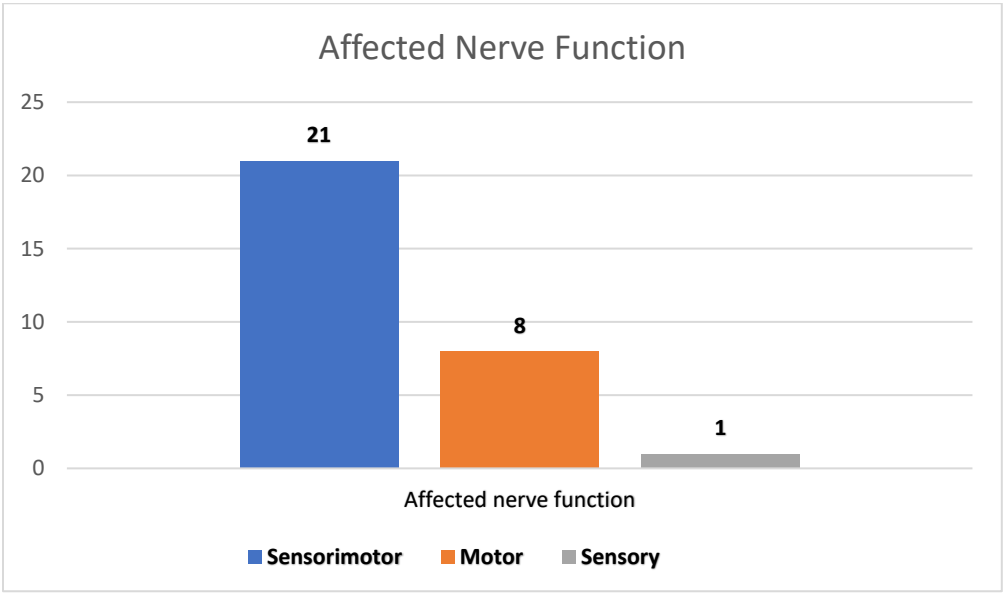

Figure 5: **The affected Nerve function in (30) patients with visceral leishmaniasis**

DISCUSSION

This study was conducted at Omdurman Tropical Teaching Hospital- Khartoum, which is a main Centre of treating VL in Sudan. During this period a lot of political issues occurred in the country that led to various limitations for the patients who lived in the suburbs to reach the Centre.

Despite the clinical spectrum of Visceral Leishmaniasis, but usually neurological presentation is not commonly associated with the infection, indeed, the affluence of neurological information of leishmania on

nervous system is clear and even ophthalmic manifestations and peripheral nervous system are not unusual . Patients with neurological symptoms during or before active visceral leishmaniasis show improvement with treatment administration [11].

Neurological symptoms such as, sensation of burning feet, foot drop, difficulty in walking, deafness, and cranial nerve deficits are mainly reported in recent publication which identified neurological abnormalities in almost forty six percent of VL patients with frequent causes of neuropathies [12].

Mustafa [11] described peripheral neuropathy in thirteen patients showed by abnormalities in the lower limbs related to foot soles hyperalgesia and legs hyperesthesia. This study found the patients with visceral leishmaniasis who possessed neurological presentation were 44% (22), the common presentation was numbness in 34% (17), and weakness in 16% (8) mainly involved the lower limbs. These findings reflect Mustafa's findings of neuropathy, but with different presentations in his article, which are sensation of burning feet, foot drop and difficulty in walking.

In addition, Hashim et al [12], conducted a cohort of 111 Sudanese patients with VL, almost half of them presented with neurological variations, most of them presented with a sensation of burning feet, and less frequent is foot drop, deafness , and multiple cranial nerve palsies.

In the same study, the authors conducted a nerve conduction study (NCS) for 15 patients and detected axonal degeneration and demyelination, which was confirmed by nerve biopsies using histopathology and electron microscopy. Indeed, in most patients who were presented with neurological manifestations, the sensory symptoms disappeared after antileishmanial therapy. The most important clinically relevant findings were the results of the nerve conduction study. The current study's test confirmed peripheral neuropathy in 60% (30/50) abnormal patients (p 0.001), which is consistent with those mentioned in international literature. Furthermore, neuropathies were axonal in type, mostly in the lower limbs (60%) (30), and with loss in sensorimotor function 70% (21), which matches those observed in Hashim et al [12], which indicate lower motor neuron pattern.

Moreover, Baetas-da-Cruz and his colleagues explain the environmental parasite persistence due to the safe target found in Schwann cells for immune evasion by Leishmania [13]. Inflammatory infiltration of peripheral nerves is associated with neuropathies, and this infiltration is induced by the activation of nuclear factor-kappa B (NFjB), which is mainly associated with infection of dermal human Schwann cell which is line with Leishmania amazonensis [14].

In Brazil, a parasitized child by Leishmania presented with neurological signs as first appeared symptoms of VL, the child presented with tremors in the hands and head, and myoclonic movements on his face, and brain image showed a diffuse reduction of the frontal lobes and cerebral atrophy [15].

In East Africa, a study with VL patients reported that parasites spread mainly into brain meninges and vessels, and the cerebrospinal fluid (CSF), but are treated after therapy [16]. In a case report by Prasad & Sen described a young boy suffering from VL for 30 months presenting with symptoms of meningitis. Lumbar puncture showed the amastigotes in the CSF [17].

Contrary to expectations, this study did not find any significance in the emergence of neurological symptoms and starting of visceral leishmaniasis (before the treatment 54.5% (12), after treatment were 45.5% (10), nor even the type of treatment, whether combination therapy or liposomal drugs (p = 0.380), (n=22) which could not be supported by previous studies.

In Sudan, a study conducted by Hussein et al [18] in adult Sudanese patients with visceral leishmaniasis from 100 patients, the authors found the common type of neuronal damage was peripheral neuropathy 4%. Furthermore, epilepsy and cranial nerves involvement were found.[-18] In contrast with Hussein et al with the current study 30/50 patients diagnosed with Peripheral neuropathy, and one patient (2%) was diagnosed with cerebral ataxia. An MRI of the brain was done for this patient and was concluded to be normal.

The patients were being followed for three weeks' duration after they completed the VL regimens, some of patients did not complete the

follow-up and died was recorded in two patients, consequently improvement was observed in 13.6% (3/22) in form of disappearance of their neurological features, while 86.4% (19/22) remained with their neurological abnormalities.

Different types of peripheral neuropathy were recorded as polyneuropathy 46.66% (14/30), mononeuropathy 23.33% (7/30), 20% (6) was poly-radiculoneuropathy, and 10% (3/30) were radiculoneuropathy.

On the other hand, 71.5% (5/7) of patients with mononeuropathy, ulnar nerve had been affected, and 28.5% (2/7) affect the peroneal nerve. The nerve functions abnormalities involved in peripheral neuropathy were 70% (21/30) sensorimotor, 26.7% (8/30) were pure motor neuropathy, and only 3.3% (1/30) was pure sensory neuropathy. The clinical presentation of peripheral neuropathy varies. 56,7% (17/30) presented with numbness, 26.7% (7/30) presented with weakness, 3.3% (1/30) presented with unsteadiness, and tremor. 26.7% (8/30) were without symptoms.

Eventually, the association between the presence of neurological symptoms in visceral leishmaniasis patients and nerve conduction study were statistically significant p 0.001.

In conjunction, these results provide an important insight into the neurological manifestations in visceral leishmaniasis patients [19]. These findings may help to better understanding the etiology of neurological involvement in patients with visceral leishmaniasis and may lead to hypothesize that chronic inflammatory response may cause axonal injury which can causes muscle weakness and neuropathic pain that affect the visceral leishmaniasis patient's life drastically.

Nevertheless, with a small sample size, caution must be applied, as the findings might not be accurate, and not all risk factors are considered, such as nourish status, and inflammatory profile.

CONCLUSIONS

Neurological presentations of Visceral Leishmaniasis infection are under reported, and peripheral neuropathy is the most common manifestation among Visceral Leishmaniasis. Subclinical neurological manifestations in neglected diseases are in higher frequency than reports, with difficulties to assess it. The study recommended conducting neurological examination for all visceral leishmaniasis patients.

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