Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.04.007

Clinical and pathological assessment of Peripheral neuropathy in pulmonary sarcoidosis

Eman M Moazen[1], Shaimaa A. Maklad[2], Rabab Yahya Abd El-kareem[3], Hoda A Eid[1], marwa mohy eldin abdelrahman ahmed[4], Heba Shoman[5], Sami A Mohamed[6], Sara A Tahoun[7], Doaa Aly Abd El-fattah[7], Enas A Farrag[7], Ola I Saleh[8], Alshimaa Ezzat A. Enayet[8], Amany Ibrahim Abosaif[6], Amal H Ibrahim[5], Ragy M Ghaly[9]

[1]Chest disease, Faculty of medicine, Al-Azhar University, Cairo, Egypt
[2] Neurology department, Faculty of medicine, Al-Azhar University, Cairo, Egypt
[3]Neurosurgery, Faculty of medicine, Al-Azhar University, Cairo, Egypt
[4] Internal medicine, Faculty of medicine, Benha University, Egypt
[5] Internal medicine, Faculty of medicine, Al-Azhar University, Cairo, Egypt
[6] Pathology, Faculty of medicine, Al-Azhar University, Domitte, Egypt
[7] Clinical pathology, Faculty of medicine, Al-Azhar University, Cairo, Egypt
[8] Radio diagnosis, Faculty of medicine, Al-Azhar University, Cairo, Egypt
[9] Chest disease, Faculty of medicine, Ain shams University
*Corresponding Author: Eman M Moazen, Chest disease, Faculty of medicine, Al-Azhar University, Cairo, Egypt
Email: emanmoazen@gmail.com

Submitted: 10 January 2023; Accepted: 14 February 2023; Published: 07 March 2023

ABSTRACT

Background: Sarcoidosis is a multifactorial disorder of unfamiliar origin characterized by noncaseating granulomas in different body parts .The purpose of this investigation was to study the association of neuropathy in patients with pulmonary sarcoidosis **Methods:** The study included 30 patients with pulmonary sarcoidosis on systemic steroid with hypoxia, 30 patients with pulmonary sarcoidosis on systemic steroid without hypoxia and 30 patients with pulmonary sarcoidosis and not on steroid without hypoxia. Clinical, neurophysiological, laboratory, radiological and histopathological assessment was done for them. **Results:** LANSS pain scale was significantly associated with the neuropathic on systemic steroids contributions group when compared to the neuropathic without steroids group. The TCNS's univariate linear regression analysis revealed statistically significant correlations between clinical, electrophysiological, and disability indicators. The mean serum levels of il-2R and ACE were greater in the sick group than in the control group (193.93 ± 56.4, 202.46 ± 351.78 for patient group and 29.1 ± 8.498884, 78.526667 ± 63.995829 in control group respectively). **Conclusion:** There was significant positive correlation in severity of neuropathy and degree of hypoxia and there were statistically significant difference between severity of neuropathy and dose of steroids in both the Initial dosage and 3-month evaluation of response.

Keywords: Peripheral neuropathy, sarcoidosis, steroid, hypoxia, High resolution computed tomography (HRCT).

INTRODUCTION

Sarcoidosis, sometimes called Besnier-Boeck-Schaumann disorder, is a condition where aberrant inflammatory cell sclusters create lumps called granulomata [1]. Typically, the lymph nodes, skin, or lungs are where the condition starts. Eyes, the liver, the heart, and the brain are less frequently impacted. Nevertheless, any organ may be impacted [2].

Distribution to the lungs is undoubtedly the most frequent manifestation of sarcoidosis. Ninety percent or more of those who are influenced have lungs intervention [3]. Generally, 50% of patients experience lungs problems that are persistent, and 5 to 15% experience progressive lungs parenchymal fibrosis [4]. Alveoli, smaller bronchi, and tiny blood arteries are all affected by the inflammation reaction in sarcoidosis of the lungs, which is largely an interstitial respiratory illness [5]. Histologically, sarcoidosis of the hearts is a reacting oedematous granulomatous inflammation with actively granulomatous inflammations. Patchy distributions of the afflicted regions is present, along with regional cardiac muscles hypertrophy [6]. This causes the heart to scar and remodel, which induces the heart cavities to enlarge and the heart musculature to thin. The condition worsens and eventually causes heart chambers aneurysms [7].

Around 9 and 37% of instances of sarcoidosis, which affects mainly African Americans than European Americans, affect the skin [8]. Erythema nodosum, plaques, maculopapular eruptions, subcutaneous lesions, and lupus pernio are among the most prevalent disorders. Since the lesions typically disappear instantaneously in 2-4 weeks, intervention is not necessary [9]. Despite the potential for disfigurement, cutaneous sarcoidosis infrequently results in serious issues. Hair loss that is diffuse or patchy is the first sign of scalps sarcoidosis [10].

Any part of the neurological system could be affected. Neurosarcoidosis is the medical term for sarcoidosis that affects the nerve system [11]. About 5–30% of instances of neurosarcoidosis damage the cranial nerves, and the most frequent neurological symptom of sarcoidosis is peripheral facial nerves palsy, which is frequently bilateral. It happens suddenly and is typically fleeting [12]. Involvements of the central nervous systems occur in 10 to 25% of instances with sarcoidosis. Optic nerves dysfunctions, papilledema, palates dysfunctions, neuroendocrine problems, hearing irregularities, hypothalamus and pituitary abnormalities, chronic meningitis, and neuropathic pain are some more typical neurosarcoidosis symptoms [13].

It is recommended to treat sarcoidosis to preserve organs functions and lessen symptoms load. Currently therapies concentrate on stopping the development and spread of granulomas [14]. A micro environmental circumstance believed to affect innate and adaptive immunity by boosting pro-inflammatory responses and to contribute to the pathogenesis of fibrotic disorders is hypoxia, which is characterized as a discrepancy between deficient tissues oxygen supply and cells demands [15]. Given that sarcoidosis granulomas are hypoxia, similar to tuberculous granulomas, due to the lack of deep vascularization, hypoxia's influence on macrophages is highly relevant to research in this disease 2022/12/19. Additionally, MD-macrophages might well be subjected to lower oxygen tensions environments from inflammation tissues to granulomas primarily as a result of O_2 intake linked to the hypermetabolisms of inflammatory cells [17]. The hypoxia-inducible factors (HIF) transcription factors and the genes that it targets that include the hypoxia-responses elements are primarily responsible for regulating the cellular responses to hypoxia [18]. While HIF-1 expressions were sporadic in sarcoidosis research, these investigations did indicate the production of HIF-targets genes within lungs and lymph nodes granulomas. It is yet unknown how hypoxia and HIF-1 signaling affect the mechanisms governing granuloma evolution, and their consequences on sarcoidosis immune cells have never been studied [19].

Typically, a sural nerve biopsy is the last phase in the diagnosis of a variety of peripheral neuropathies. Due to its intrusive nature, it is only used in situations that persist despite intensive exercise. If it is effective, however, it may change the course of future therapeutic options [20]. The area of cutaneous numbness at the lateral foot edge, where the sural nerve once usually affected, is the primary result of biopsies. For individuals with vasculitis getting corticosteroids treatment, main problems including neuroma development or wound infections happen in 1% of cases, which may prolong rehabilitation [21]. Although it has been shown and established that only a small

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number of peripheral neuropathies requiring biopsy, in rare circumstances the process could be essential for diagnosis [22]. Presently, the evaluation of curable reasons of neuropathy is the primary justification for nerve biopsies. In practise, this method is especially helpful for identifying interstitial neuropathic pain, including those caused by vasculitis, granulomatosis, leprosy, amyloidosis, or tumours, as well as for confirming a chronic inflammatory demyelinating polyneuropathies with unusual presentations [23].

Axonal transportation requires energy because it depends on oxygen for peripheral nerve activity, and hypoxia causes axonal degenerations [24]. Peripheral neuropathy and the length and intensity of hypoxemias are connected [25]. Since separated nocturnal hypoxia causes the breakdown of adenosines monophosphates and the subsequent creation of adenines nucleotides, which are implicated in the formation of free oxygen radicals after reoxygenations, oxidative stress could be a major factor in hypoxia-related neuropathy [25]. Furthermore, increased nodal excitability and decreased propagation velocities can result from the oxygen-dependent Na-K-decreased ATPase's activities [26].

Ninty percent of sarcoidosis suferrers experience thoracic radiography problems at a certain point, and twenty percent of individuals acquire chronic lung illness that results in pulmonary fibrosis. Whereas computed tomography (CT) seems to be more effective for the identification of adenopathy and mild parenchymal illness, radiograph is frequently the first diagnostic imaging investigation in individuals who have pulmonary dysfunction [27].

There are several radiography characteristics that can indicate pulmonary sarcoidosis: The most frequent observation is bilateral hilar lymphadenopathy enlargements, accompanied by interstitial pulmonary disease. The most common observations of lung activation with higher-resolutions CT are bilateral perihilar opacities, fibrotic alterations, and micromodels with perilymphatic distributions. A typical symptoms, including aspergillomas and sequelae such honeycomb-like tumors, allied military aperture settings, mosaics attenuations, tracheobronchial involvements, and pleural illness, might also be present [27]

Therefore the aim of the current study was to demonstrate the association of cranial and peripheral neuropathy sensory, motor neuropathy, mononeuritis multiplex or polyradiculopathy in patients with sarcoidosis as well as assessment the effect of steroid and hypoxia on developing it.

Patients and Methods

This was a case control study with a non-random purposive sampling technique. The current study was performed at >>>>> hospital from >>>> to >>>> for six months. The current study included 30 patient (patients group) with pulmonary sarcoidosis, detected on HR CT, on systemic steroid with hypoxia (either with or without respiratory failure), pulmonary sarcoidosis on systemic steroid without hypoxia and 30 patient (control group) with pulmonary sarcoidosis and not on steroid.

Inclusion criteria: Subjects above 18 years from both sex with pulmonary sarcoidosis were included in the study.

Exclusion criteria: Subjects under 18 years, known to have chronic lung disease other than sarcoidosis, or other causes of peripheral neuropathy as diabetes, hereditary or metabolic neuropathy were excluded from the study.

Data collection and instruments

All subjects were subjected to:

The socio-demographic and clinical characteristics: Full history taken with special emphasis on disease duration, steroid use, its duration, dose and types. By means of a short questionnaire that asked questions about age and gender, the sampling population's socio-demographic variables were ascertained. According to clinical examinationall patients had their chest and systemic been examined as well as neurological assessment.

Neurophysiological assessment: The examination of the motor and sensory conduction velocities in all four limbs was done using electrophysiological studies. Standard techniques were used to evaluate the nerve and muscle compound action potentials, nerve conduction velocity, distal motor and F-wave latencies. The body's temperature was managed. Standard methods were used to undertake sural, superficial peroneal, median, radial, and ulnar sensory nerve conduction tests. Peroneal, posterior tibial, radial, median, and ulnar nerves on both sides were studied as part of the motor system. Antidromically recorded sensory action potentials (SAPs) were used. The near-nerve needle technique was utilised when SAPs could not be detected by surface electrodes. Using a

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monopolar needle, an electromyographic assessment of the muscles in the clinically afflicted regions was carried out. Severity was assessed according to the two scales mentioned above (LANSS pain and Toronto clinical neuropathy scoring system scale).

LANSS pain scale: LANSS pain scale translated into Arabic for use in neuropathy assessments. A rating of 12 or higher on the LANSS pain scale designates pain that is controlled by neuropathic processes (LANSS $\geq$ 12 grouping), while a score of <12 designates pain that is not indicative of neuropathic processes. On a numeric assessment scale from 0 (no pain) to 10, the participants were requested to rate their mean level of pain during the previous month (extreme pain).

The seven-items LANSS Pain Scale consists of five yes/no queries that participants answered about whether they had sensory experiences during the earlier week (dysaesthesias, autonomic dysfunctions, evoked pain, paroxysmal pain, and thermal pain), and two items depending on a bedside investigation that doctors answered (allodynias and pinpricks thresholds). The highest allowable scoring was 24, and each item's weighting grading was dependent on the odds ratio (OR) that had been previously established for each item's known associations with neuropathic pain. 22 "Yes" responses to the questions about dysaesthesia and autonomic dysfunctions received a score of 5 apiece. The ratings for proximal pain, thermal pain, and evoked pain were 3, 2, and 1, correspondingly. A 5 was given for allodynia and a 3 for altered pinpricks thresholds. It has been established that a LANSS Pain Scoring system of 12 or below is a suitable cutoff for identifying individuals with neuropathic pain. This cutoff was utilized to distinguish individuals with neuropathic pain from those with nociceptive pain alone. The physicians at the consultation documented each participant's treatment choice after they had completed the LANSS Pain Scale.

The original structures of the LANSS English edition were preserved when translating it using routinely employed algorithms in compliance with international standards. The translating into Arabic was done by two doctors who are both fluent in English: one pain specialist and one psychiatrist.

To assess the stability of the pain scale, the same chronic pain specialist retested the participants after two weeks. The same researcher consistently used the measure while remaining unaware of the disease outcomes shown by the LANSS scores.

Toronto clinical neuropathy scoring system (TCNS): The Toronto Clinical Neuropathy Scoring System (TCNS), a further instrument that measures the existence and severity of peripheral neuropathy, is a standardized scale [28, 29]. The assessment, which encompasses sensory and motor complaints in addition to lower-limbs sensory and reflexes observations that are part of the usual clinical assessment of patients with neuromuscular diseases, runs from a minimal of 0 (no neuropathy) to a maximal of 19 points. The indicators of peripheral neuropathy include tingling, numbness, discomfort, weakening, ataxias, and upper-limbs symptoms. These ailments are evaluated as present or absent. The following symptoms are also regarded as peripheral neuropathy symptoms: lights touches, pinpricks, temperatures, location, and vibrations assessed as normal or abnormal at the toes. Across both sides, the knees and ankles reflexes are categorised as normal, diminished, or absent [29]. It is possible to evaluate the severity of peripheral neuropathy as follows: 0-5, no or minimum peripheral neuropathy; 6–8, mild peripheral neuropathy; 9–11, moderate peripheral neuropathy; and $\geq$ 12, severe peripheral neuropathy [30]. For this investigation, a TCNS of 1–5 was regarded as being indicative of mild peripheral neuropathy.

Measurements and markers: The arterial blood gases (PH, Paco2, Pao2, Osat) were measured in all diagnostic categories. Serum sIL-2R was evaluated using a two-site chemiluminescent enzymatic immunometric test (SRL, Tokyo, Japan), and serum ACE was assessed using a colorimetric technique with p-hydroxyhippuryl-l-histidyl-l-leucine as the substrates (BML, Tokyo, Japan). The manufacturer reports that concentrations of ACE and sIL-2R that were greater than 25 U/L and 543 U/mL, respectively, compared to the healthy group. As a result, concentrations above the cut - off values of 25 U/L for ACE and 543 U/mL for sIL-2R were deemed high.

Nerve biopsy by sural nerve biopsy as well as Pathological analysis of nerve biopsy: A nerve biopsy was carried out in a region that had recently experienced therapeutically significant damage after the participants' informed consent had been acquired. With the exception of one Patient, who received sural nerves biopsies without muscular

samples, the superficial peroneal nerves and the peroneus brevis muscles were both collected at the same operation.

The nerve samples were preserved at 4°C in a buffered solution of 3.6% glutaraldehyde at pH 7.4. One nerve fragment was sliced at a thickness of 5 mm and fixed in paraffins. We looked at sequences labeled with Masson's trichrome and H&E (haematoxylins and eosins). Additional fragment was embedded in epon and postfixed in 1% osmium tetroxides in buffers for 3 hours at 4°C. For morphometry, thionin-stained transverse slices (1 mm thick) were employed, and for electron microscopy, portions (0.1 mm thick) labelled with uranyl acetates and leads citrates were used. On 1-mm thick slices, the density of myelinated fibres was estimated and compared to experimental controlled values.

In order to conduct immune-pathological tests, nerve pieces were quickly frozen in liquid nitrogen. To identify specific cells subsets, nerves segments with noticeable inflammatory infiltrates on H&E staining were identified. On frozen and/or paraffins-embedded samples from patients whose nerves biopsies findings revealed inflammatory infiltrates, cellular infiltrates were immune-labeled. The ubiquitous leucocytes antigens CD68, CD3, CD4, CD8, and CD20 were targeted using monoclonal antibodies.

A nerve fragment was post-fixed in osmium tetroxides, macerated in 66% glycerin for 48 hours, and then dissected in pure glycerin to conduct a teased fibre research. Over more than 10 internodes, 100 consecutive nerves fibres were separated and categorised based on their shape.

Following staining serial slices with H&E and Masson's trichrome, paraffins-embedded muscles samples collected via biopsies of the peroneus brevis muscles during the nerves biopsy technique were investigated. The neighbourhood ethics committee granted permission for this content to be used.

CT chest scan: High resolution computed tomography (HRCT) was performed on all participants to look for pulmonary abnormalities. At the AlZahraa hospital, a high resolution Computed tomography of the chests was performed using a Toshiba Aquilion Prime-160 slice-Japan. The patient was instructed to hold his breath and not move during the scanning. This lasted less than 30 seconds, after a scout acquisition had been made in AP from the roots of the necks to the abdominal area. In order to analyse the pulmonary parenchyma with two windows width of 1000 HU, thin axial slicings were acquired throughout fully inspiration with a thicknesses varying from 0.5 to 1.5 mm. The images were then reconstructed with higher resolution matrices of 512x512. A frame of about 30 to 50 HU, a breadth of 400 HU, 120 Kvp, and automatically regulated amperages were used to examine the mediastinum (120-259 mA). There was no administration of iodine - based contrasted medium intravenously. A separate work station received the images for sagittal and coronal reconstructions.

Statistical analysis: SPSS (Statistical Package for Social Science) version 22 was used for data entry and analysis. Numbers, percentages, means, standard deviations, medians, and ranges were used to present the data. To contrast between qualitative variables, the chi-square test and the Fisher Exact testing were utilized. Unbiased samplings Paired Samples and the t-test were employed to compare numerical variables between the groupings. To compare quantitative factors between before and after therapy, a t-test was used. The parameters of the LANSS scale were determined using factor analysis for dichotomous datasets (latent trait modeling), when $P< 0.05$, a P-value is deemed statistically significant.

RESULTS

The current study included 60 patients. Their age mean was 47.2 ± 8.397 ranging from 34 to 65 years. The majority of patients were females and not smokers (83.3%).

Twenty six patients (43.3%) had Inhaled corticosteroid with duration mean 2.8 ± 5.391. all patients had oral corticosteroid. Patients having skin lesion, pulmonary disease, lymphadenopathy, hepatosplenomegaly, heart disease and thyroid nodule represented 23.3, 96.7, 83.3, 33.3 and 6.7% respectively. The bulk of patients (80%) represented stage 2. Ninety percent of patients were diagnosed by biopsy. Half of participants had airway involvement and 86.7% of them had eye lesion (Table 1, figure 1).

All elements were discovered to be significantly correlated with the neuropathic on systemic steroids contributions group when compared to the neuropathic without steroids group. The ORs for individual LANSS Pain Scale items were estimated in order to characterize the relative likelihoods of

each item's incidence in the neuropathic on systemic steroids contributions group (patients group) relative to its occurrences in the neuropathic without steroids grouping (Table 2). The strongest difference between the neuropathic and nociceptive groupings was allodynia (OR 61.3), which was preceded by dysaesthesia (OR 27.6).

As shown in Table 3, the TCNS's univariate linear regression analysis revealed statistically significant correlations between clinical, electrophysiological, and disability indicators. Weak connections between grip strength and the TCNS were found, as were usually modest correlations between the TCNS and the electrophysiological results and disability scores. No statistically significant correlation between the TCNS and small-nerve fibre tests was found.

The study groups' laboratory data are displayed in table 4. It was noted that the control group's mean values for HB g/dl, AST U/L, and LDL mg/dl were greater than those of the patients group. The mean serum levels of il-2R and ACE were greater in the sick group than in the control group (193.93 ± 56.4, 202.46 ± 351.78 for patient group and 29.1 ± 8.498884, 78.526667 ± 63.995829 in control group respectively).

Table 5 showed the correlation between severity of neuropathy and degree of hypoxia. It has been noticed that there was a positive strong correlation (0.29) with a significant difference (p=0.04) between severity of neuropathy and degree of hypoxia.

Table 6 illustrated the correlation between severity of neuropathy and dose of steroids. Patients go through all of the different doses shown. It has been noticed that there was a statistically significant difference between severity of neuropathy and dose of steroids in both the Initial dosage and 3-month evaluation of response (0.02, 0.01 respectively).

Epineurial granulomas and perineurial inflammation infiltrates with varied, asymmetric involvements of nerves fascicles and axons loss were seen in all participants' histopathological examinations (Figure 2).

In the majority of patients, the number of Buenger's bandings and the density of nerves fibres differs widely between nerves fascicles, with a significant share of fibres in different phases of Wallerian degenerations.

Infiltrates predominated in the subperineurial area and surrounding endoneurial capillaries in nerves samples with mild endoneurial infiltrates. On electrons microscopy, it was discovered that mononuclear cells also attached to the endothelium of certain capillaries and occasionally blocked the lumens (Figures 2, 4 and 5).

The non - myelinated fibres were also impacted, and on electron microscopy, their density reduced approximately in tandem with that of the myelinated fibres. According to immunohistochemical labellings, macrophages and T lymphocytes predominated among the infiltrates. The great bulk of the cells in the granulomas were CD68+ macrophages. The monoclonal anti-CD68 antibodies additionally prominently adorned multinucleated giant cells that are created when active macrophages fuse (Fig. 3). The ratio of CD4+ T cells to CD8+ cells was greater, consistent with a delayed-type hypersensitivity reactions.

HRCT findings:

Pulmonary changes were interstitial lung changes as micronodules with a perilymphatic distribution, fibrotic changes, and bilateral perihilar opacities. Less likely atypical manifestations, such as mass like or alveolar opacities, honeycomb-like cysts, miliary opacities, mosaic attenuation.some patients show bilateral hilar lymph node enlargement and paratracheal lymph nodal enlargement.

DISCUSSION

Sarcoidosis is a multisystem condition defined by the existence of non-caseating granulomas that are infrequently identified in nerve biopsy specimens. Peripheral neuropathy is a rare but curable manifestation of this condition [31]. The current study included aimed at studying the association of cranial and peripheral neuropathy sensory, motor neuropathy, mononeuritis multiplex or polyradiculopathy in patients with sarcoidosis as well as assessment the effect of steroid and hypoxia on developing it.

The study included 30 patients (patients group) with pulmonary sarcoidosis on systemic steroid with hypoxia (either with or without respiratory failure), pulmonary sarcoidosis on systemic steroid without hypoxia and 30 patients (Control group) with pulmonary sarcoidosis and not on steroid. Their age mean was 47.2 ± 8.397 ranging from 34 to 65 years. The majority of patients were females and not smokers (83.3%).

The current study agreed with another study done by M Ishihara et al, [32] on Japanese Sarcoidosis which demonstrated that the sarcoid uveitis individuals were divided into 13 men and 39 females, with an average age of 58.8 ± 15.2 years.

This was in conflict with another study done by A Abraham et al [33] who stated that the mean age of the included sarcoidosis patients was 59 ± 13, which is higher than that in the current study, and male preponderance (62%).

The current study indicated that all LANSS pain scale were discovered to be significantly associated with the neuropathic on systemic steroids contributions group when compared to the neuropathic without steroids group. The strongest difference between the neuropathic and nociceptive groupings was allodynia (OR 61.3), which was preceded by dysaesthesia (OR 27.6).

Another study done by W El Sissi et al, [34] was in agreement with the current study. It has been noticed that the individual LANSS Pain Scale elements' discriminative validity, as determined by their ORs, was significantly greater than in the initial LANSS Pain Scale validation research [35]. For instance, in the initial validation study, the OR for neuropathy pain among individuals with allodynia was 61.2 and 5.5. This difference's cause is unknown, however it could be connected to the original sampling's diagnostic heterogeneity and the small sample size (n = 30) [35]. Additionally, it's probable that people with chronic LBP will respond to the LANSS Pain Scale more favourably than those with other chronic conditions. In the chronic LBP investigation by Kaki et al., considerably higher ORs were also recorded for specific LANSS Pain Scale items, which is consistent with the current study [36] In both the current investigation and the study by Kaki et al., [36] it needs to be emphasized that the LANSS Pain Scale was the sole tool used to diagnose neuropathic pain, no other tests.

According to the current study, the TCNS's univariate linear regression analysis revealed statistically significant correlations between clinical, electrophysiological, and disability indicators. Weak connections between grip strength and the TCNS were found, as were usually modest correlations between the TCNS and the electrophysiological results and disability scores. No statistically significant correlation between the TCNS and small-nerve fibre tests was found.

The current result agreed with a study done by [33] who found that Given their weak correlation with other neuropathic scores in individuals with polyneuropathy and reduced glucose tolerance, the TCNS's lack of correlation with smallfiber measurements is not unexpected [37], indicating that a measure that just measures small-fiber functioning may be more useful in a small-fiber polyneuropathy that is separated. However, modest to moderate correlations of the TCNS were detected in individuals with idiopathic polyneuropathy, possibly because this kind of polyneuropathy is primarily sensory, which was in agreement with the current investigation.

In the current study, it was noted that the control group's mean values for HB g/dl, AST U/L, and LDL mg/dl were greater than those of the patients group. The mean serum levels of il-2R and ACE were greater in the sick group than in the control group (193.93 ± 56.4, 202.46 ± 351.78 for patient group and 29.1 ± 8.498884, 78.526667 ± 63.995829 in control group respectively).

It has been noticed that there was a positive strong correlation (0.29) with a significant difference (p=0.04) between severity of neuropathy and degree of hypoxia.

It has been noticed that there was a statistically significant difference between severity of neuropathy and dose of steroids in both the initial dosage and 3-month evaluation of response (0.02, 0.01 respectively).

This agreed with a previous report done by Ishihara et al [32] who concluded that 69.2% of individuals with sarcoid uveitis, 5.4% of individuals with non-sarcoid uveitis, and 16.7% of individuals with PIOL had higher serum sIL-2R levels. An enhanced sIL-2R concentration had a sensitivity of 69.2% and a specificity of 93.0% for detecting sarcoidosis. Contrarily, individuals with sarcoid uveitis were the only ones whose serum ACE concentrations were raised, with a sensitivity of 44.2% and specificity of 100%. Additionally, more individuals (75.0%) with sarcoid uveitis had increased blood sIL-2R and/or ACE levels than those (44.2%) with increased serum ACE levels solely (P = 0.0025). Increased sIL-2R and/or ACE had a sensitivity and specificity of 75.0% and 93.0%, respectively, for diagnosing sarcoid uveitis. The PPV and NPV were both 0.87.

The current study emphasized that there was a positive strong correlation (0.29) with a significant

difference (p=0.04) between severity of neuropathy and degree of hypoxia.

This agreed with a study done by Avci et al. [38] who stated that in line with earlier studies, there was a correlation between axonal neuropathy, hypoxic measures, and nerves conductions in sarcoidosis sufferers [39-41]. These research also revealed that the amplitudes of sensory and mixed nerves actions potentials is smaller in individuals with severe sarcoidosis, minimum SaO2 ≤80%, and ST90, while the sural nerve velocities is less in individuals with sarcoidosis [39, 42]. Additional survey suggests COPD patients to have less often occurring demyelination and hypoxia-associated axonal degenerations [43]. Since sarcoidosis therapy showed that the altered nerve functioning was somewhat recoverable, these pathophysiological modifications in nerves injury are more functionally than structurally [40, 44].

In contrast to our study, Evlice et al. [45] reported a reduction in tibial CMAP amplitudes and a slower tibial NCV in the sarcoidosis cohort, but no relationship between the intensity of sarcoidosis, minimum SaO2, and neuropathy was discovered. Contrary to the current study, the sarcoidosis sufferers were older, and the investigators' definition of hypoxia only included the minimum SaO_2 concentration [45].

Disorders associated with hypoxia have a complicated origin. Hypoxia and hypercapnia are brought on by the occasional upper airway obstructions in sarcoidosis sufferers. In addition to adverse morphological alterations, hypoxia promotes metabolic abnormalities, systemic inflammations, endothelial dysfunctions, and vascular diseases [46-48]. Nearly 95% of people with COPD who have hypoxia have electrophysiology problems [49]. Uncertainty surrounds the pathogenesis of the impairments in nerves conductions found in sarcoidosis sufferers. The correlation between peripheral neuropathy and sarcoidosis has a number of plausible causes. An significant factor in hypoxia-induced neuropathy is oxidative stress. Due to nerve edoema, endoneurial hypoxia causes a greater intercapillary distances [50]. Hypoxic neuropathy results in endothelial cells hyperplasia and hypertrophy as well as a thickening of the nerves capillary basal membranes. These microvascular angiopathic alterations impair the delivery of nutrients and oxygenation, affect neuronal function, and put the patient at risk for vascular occlusions and capillaries lumen narrowing [51]. Additionally, the sarcoidosis-related higher-frequency intermittent hypoxia is characterised by oxidative stress and reactive oxygen compounds production and a reoxygenation and hypoxemia cycling akin to ischemia-reperfusion destruction. When there is significant hypoxia, the process of ischemia and reperfusion causes tissues acidosis, and intracellular sodium and calcium buildup damages the sarcolemma [52]. Moreover, damages to the central nervous system caused by hypoxia have been linked to an excitotoxicity process controlled by excitatory amino acids residues. This excitotoxicity is assumed to be connected to the energy metabolisms brought on by oxidative stress, which results in neurodegenerations [53]. Lastly but not least, hypoxic nerves become resistant to ischemia conduction blockage (RIBC) as a result of a decreased need for energy and an improved anaerobic glycolysis effectiveness [54]. It is believed that therapy can partially reverse RIBC. Exposures to chronic, acute intermittent hypoxia frequently cause RIBC, which causes axonopathies. The development of RIBC is the outcome of an adaptive strategy that is dependent on a critical level of microvascular abnormalities and nocturnal oxygen desaturations [54]. A high sensitivity to peripheral nerves damage is a result of a combination of alterations in sarcoidosis-related hypoxia.

CONCLUSION

The current study concluded that there was an association of cranial and peripheral neuropathy sensory, motor neuropathy, mononeuritis multiplex or polyradiculopathy in patients with sarcoidosis. There was a positive strong correlation with a significant difference between severity of neuropathy and degree of hypoxia. There was a statistically significant difference between severity of neuropathy and dose of steroids in both the Initial dosage and 3-month evaluation of response.

DECLARATIONS

Ethics approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and materials: All data and materials are fully presented in the manuscript.

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

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions

The study Conceptualization was done by Eman M Moazen. Data curation was carried over by Shaimaa A. Maklad. Formal analysis was carried over by Rabab Yahya Abd El-kareem. Funding acquisition was done by Hoda A Eid. Investigation was done by marwa mohy eldin abdelrahman ahmed. Methodology was done by Heba Shoman. Project administration was done by Sami A Mohamed. Resources were done by Sara A Tahoun. Software was done by Doaa Aly Abd El-fattah. Validation was done by Enas A Farrag. Visualization was done by Ola I Saleh. Writing-original draft was done by Alshimaa Ezzat A. Enayet and Amany Ibrahim Abosaif. Writing-review and editing were done by Amal H Ibrahim and Ragy M Ghaly. All authors read and approved the final version of the manuscript.

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Figure legends

Figure (1): Histogram of age distribution among studied cases

Figure (2): Multifocal neuropathic sufferer's muscles biopsies displaying two sizable multinucleated giant cells encircled by a mononuclear inflammatory infiltration. H&E stain. Scale bar= 50 mm.

Figure (3): Skin biopsy demonstrating the numerous multinucleated giant cells typical of sarcoidosis from a patient with mononeuropathy and a skin lesions on the leg. H&E staining Scale bar= 50 mm.

Figure (4): Sarcoid granuloma found in a patient with multifocal neuropathy following a nerve biopsy. Anti-CD68 monoclonal antibody labelling of macrophages to display their massive confluents decorations of enormous cells Scale bar= 50 mm.

Figure (5): Multifocal neuropathic participant's endoneurial granulomas. Stained with thionin blue Scale bar= 50 mm.

Figure (6): Vasculitis without necrosis and multinucleated large cells in epineurial granulomas. The H&E stain. Scale bar= 30 mm.

Figure (7): A patient with multifocal sarcoid neuropathy had muscular biopsy, which revealed necrotizing vasculitis, which is frequently linked to neurological consequences of sarcoidosis. The H&E stain. Scale bar= 100 mm.

Figure (8): (A, D) investigation of the tibial nerves' conduction velocity. Stimulation in the popliteal fossa resulted in conduction block configurations in both nerves. The left tibial nerve's conduction block was discovered using the inching methodology 9–11.5 cm from the ankle joint (22.5-25 cm distal to the popliteal fossa). (B) The left tibial nerve showed no obvious F-waves, along with (E) a delayed F-wave latency in the right tibial nerve.

NCV: nerve conduction velocity, CMAP: compound muscle action potential.

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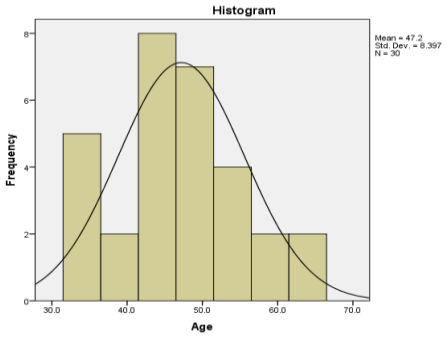

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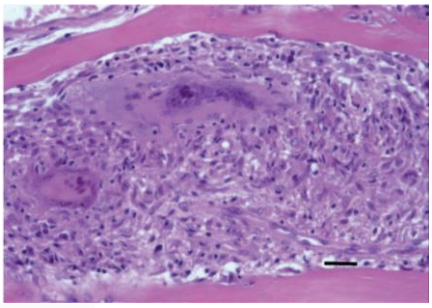

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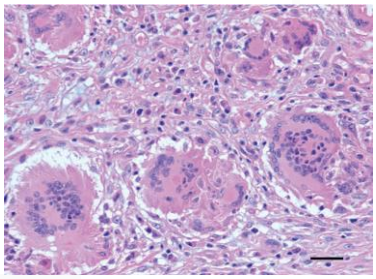

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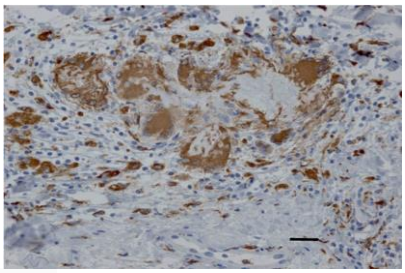

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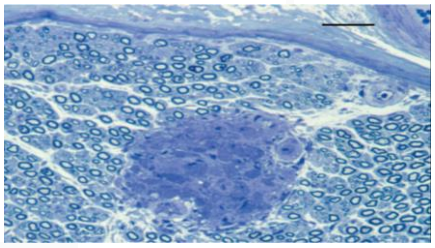

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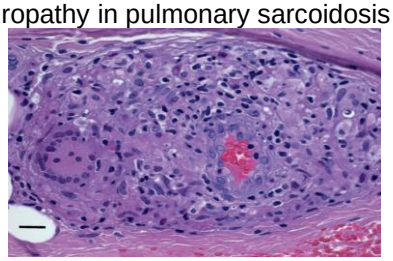

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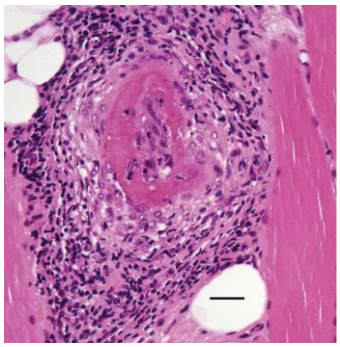

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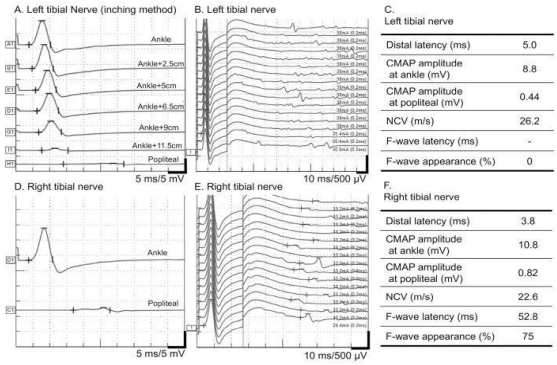

C. Left tibial nerve

Distal latency (ms)	5.0
CMAP amplitude at ankle (mV)	8.8
CMAP amplitude at popliteal (mV)	0.44
NCV (m/s)	26.2
F-wave latency (ms)	-
F-wave appearance (%)	0

F. Right tibial nerve

Distal latency (ms)	3.8
CMAP amplitude at ankle (mV)	10.8
CMAP amplitude at popliteal (mV)	0.82
NCV (m/s)	22.6
F-wave latency (ms)	52.8
F-wave appearance (%)	75

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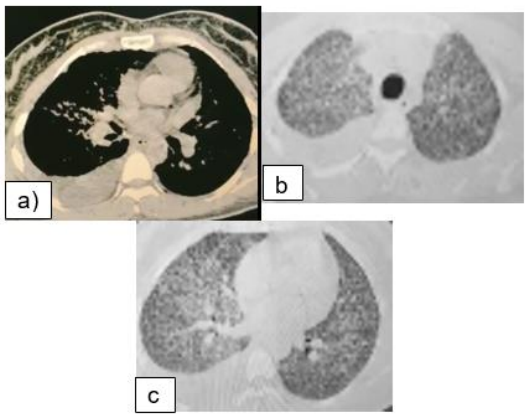

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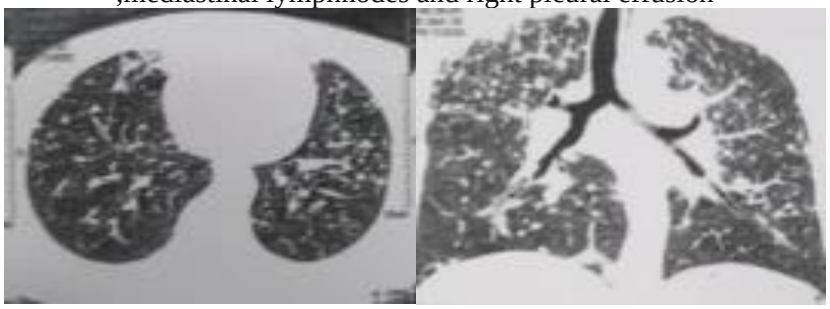

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Table (1): Demographic and clinical characteristics of the studied patients:

Parameter	**N=60**		**P-value**
Age	Mean ± SD	47.2 ± 8.397	
	Media (Min-Max)	47 (34 – 65)	
Sex	Male	10 (16.7)	<0.001
	Female	50 (83.3)	
Smoking	Smoker	10 (16.7)	<0.001
	Not a smoker	50 (83.3)	
	Duration (month)	38.233 ± 42.58	
Inhaled corticosteroid	Yes	26 (43.3)	0.465
	No	34 (56.7)	
	Duration (month)	2.8 ± 5.391	
Oral corticosteroid	Yes	60 (100)	-
	No	0	
	Duration (month)	11.172 ± 7.915	
Skin lesion	N (%)	14 (23.3)	0.003
Pulmonary disease	N (%)	58 (96.7)	<0.001
Lymphadenopathy	N (%)	50 (83.3)	<0.001
Hepatosplenomegaly	N (%)	20 (33.3)	0.068
Heart disease	N (%)	14 (23.3)	0.003
Thyroid nodule	N (%)	4 (6.7)	<0.001
Stage	Stage 1	2 (3.3)	<0.001
	Stage 2	48 (80)	
	Stage 3	6 (10)	
	Stage 4	4 (6.7)	
Diagnosed by	Bal	6 (10)	<0.001

	Biopsy	54 (90)	
Airway involvement	Yes	30 (50)	1
	No	30 (50)	
Eye lesion	Yes	8 (13.3)	<0.001
	No	52 (86.7)	

Table (2): Risk assessment of each element on the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale and its connection to the ultimate determination of the kind of pain experienced by sarcoidosis individuals (data from 60 patients)

	Patient (n=30)	**Control (n=30)**	**OR**	**95% CI**
Dysaesthesia			27.6	17.4, 44.7
Present	24 (80)	20 (66.67)		
Absent	6 (20)	10 (33.33)		
Autonomic dysfunction			17.3	9.7, 31.7
Present	18 (60)	16 (53.33)		
Absent	12 (40)	14 (64.67)		
Evoked pain			17.6	13.0, 24.7
Present	20 (66.67)	17 (56.67)		
Absent	10 (33.33)	13 (43.33)		
Paroxysmal pain			2.6	1.9, 4.4
Present	22 (73.3)	16 (53.33)		
Absent	8 (26.67)	14 (64.67)		
Thermal pain			2.7	2.1, 4.4
Present	19 (63.33)	13 (43.33)		
Absent	11 (36.67)	17 (56.67)		
Allodynia			61.3	40.0, 94.7
Present	20 (66.67)	11 (36.67)		
Absent	10 (33.33)	19 (63.33)		
Altered pinprick threshold			11.6	8.6, 16.3
Present	21 (70)	14 (64.67)		
Absent	9 (30)	16 (53.33)		

Data presented as numbers of patients and percentage. aLANSS Pain Scale score ≥ 12 identified patients with a neuropathic on systemic steroid contribution to their pain compared with those without steroid. OR, odds ratio; CI, confidence interval.

Table (3): Toronto Clinical Neuropathy scoring univariate correlation coefficients with clinically and electrophysiological measurements

Characteristic	**R**	**P**
Grip (right)	-0.26	<0.01
Grip (left)	-0.30	<0.001
Nerve conduction studies Median – sensory		
Amplitude (μV)	-0.48	<0.0001
Velocity (m/s)	-0.37	<0.0001
Median – motor		
Amplitude (μV)	-0.29	<0.001
Velocity (m/s)	-0.49	<0.0001
Sural		
Amplitude (μV)	-0.59	<0.0001
Velocity (m/s)	-0.49	<0.0001
Peroneal		
Amplitude (μV)	-0.40	<0.0001
Velocity (m/s)	-0.49	<0.0001
Tibial		
Amplitude (μV)	-0.58	<0.0001
Velocity (m/s)	-0.57	<0.0001
VPT (V)		

Finger	0.52	<0.0001
Toe	0.57	<0.0001
Laser Doppler flare imaging	0.17	0.33
Cooling detection threshold	0.17	0.32
Warm detection threshold	0.16	0.37
Upper extremity function	-0.42	<0.0001
Lower extremity function	-0.54	<0.0001

ONLS, Overall Neuropathy Limitations Scale; RODS, Rasch-built Overall Disability Scale; VPT, vibration perception threshold.

Table (4): Lab data of the studied groups:

	Patient (n=30) (Mean ± SD)	Control (n=30) (Mean ± SD)
HB g/dl	10.54 ± 0.5379	12.693333 ± 1.295598
platelet count x103/ul	309.967 ± 121.369	268.966667 ± 68.473243
urea mg/dl	27.127 ± 6.766	27.9 ± 5.642205
AST U/L	27.4 ± 7.214	29.1 ± 5.221639
ALT U/L	24.5 ± 7.77	22.666667 ± 3.526582
LDL mg/dl	140.83 ± 70.396	120.833333 ± 42.831734
Serum glucose mg/dl	114.7 ± 42.15	89.266667 ± 8.513411
ACE U/L	193.93 ± 56.4	29.1 ± 8.498884

Data represented as Mean ± SD.

Table (5): Correlation between severity of neuropathy and degree of hypoxia (n=30)

Degree of hypoxia	Severity of neuropathy				R	P
	Minimal (0–5)	Mild (6–8)	Moderate (9–11)	Severe (>11)		
Normal (80–100 mm Hg)	0	0	1 (3.33)	1 (3.33)	0.29	0.04
Mild (60–80 mm Hg)	0	1 (3.33)	1 (3.33)	2 (6.67)		
Moderate (40–60 mm Hg)	1 (3.33)	2 (6.67)	1 (3.33)	3 (10)		
Severe <40 mm Hg)	2 (6.67)	4 (13.33)	4 (13.33)	7 (23.33)		

Data was expressed as n (%). P- value significant if <0.05.

Table (6): Correlation between severity of neuropathy and dose of steroids (n=30):

Dose of steroids	Severity of neuropathy				R	P
	Minimal (0–5)	Mild (6–8)	Moderate (9–11)	Severe (>11)		
Initial dosage					0.33	0.02
40 mg/day^{-1}	1 (3.33)	2 (6.67)	1 (3.33)	5 (16.67)		
30 mg/day^{-1}	1 (3.33)	4 (13.33)	3 (10)	4 (13.33)		
20 mg/day^{-1}	1 (3.33)	1 (3.33)	3 (10)	4 (13.33)		
3-month evaluation of response					0.27	0.01
15 mg/day^{-1}	0	1 (3.33)	1 (3.33)	2 (6.67)		
10 mg/day^{-1}	1 (3.33)	1 (3.33)	1 (3.33)	5 (16.67)		
7.5 mg/day^{-1}	1 (3.33)	2 (6.67)	4 (13.33)	5 (16.67)		
Taper to 0 mg/day^{-1}	1 (3.33)	3 (10)	1 (3.33)	1 (3.33)		

Data was expressed as n (%). P- value significant if <0.05.