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Widespread sensory neuropathy in diabetic patients hospitalized with severe COVID-19 infection

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ABSTRACT

Aims: To characterize the distribution and severity of sensory neuropathy using a portable quantitative sensory testing (QST) device in diabetic patients (DM) hospitalized with severe COVID-19 infection.

Methods: Four patients with diabetes and severe SARS-CoV-2 requiring non-invasive ventilation for a protracted duration underwent clinical, laboratory and radiologic assessment and detailed evaluation of neuropathic symptoms, neurological assessment, QST on the dorsum of the foot and face using NerveCheck Master with assessment of taste and smell.

Results: All four subjects developed neuropathic symptoms characterized by numbness in the feet with preserved reflexes. QST confirmed symmetrical abnormality of vibration and thermal thresholds in both lower limbs in all patients and an abnormal heat pain threshold on the face of two patients and altered taste and smell.

Conclusions: Severe COVID-19 infection with hypoxemia is associated with neuropathic symptoms and widespread sensory dysfunction in patients with DM.

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1. Introduction

COVID-19 was declared a pandemic by the World Health Organization in March 2020. The clinical manifestations of COVID-19 include fever, difficulty breathing, diarrhea, muscle pain, fatigue and loss of smell and/or taste. Neuronal involvement of SARS-CoV2 has been highlighted with reports of altered taste, smell and hearing as well as neuropathic pain in patients with COVID-19 pneumonia [1,2,3]. In a case series of 214 patients, 36% had neurological symptoms which were associated with more severe illness and higher mortality [1]. A wide spectrum of neurological complications have been described and include acute cerebrovascular disease, impairment of consciousness, meningitis and encephalopathy, ataxia, seizures, skeletal muscle injury and neuropathic pain [4,5] as well as Guillain-Barre syndrome [6].

The propensity for corona viruses (Co-Vs) to affect neurons is established for SARS-CoV1 and MERS-CoV [7]. Transgenic
mice have shown that MERS-CoV [7] when given intranasally enter the brain via the olfactory nerves and rapidly spread to the thalamus and brainstem. There is also evidence that CoVs may first invade peripheral nerve terminals and gain access to the CNS via a synapse-connected route [8,9]. Viral antigens have been detected in the brainstem in the nucleus of the solitary tract and nucleus ambiguous which receive sensory information from the mechanoreceptors and chemoreceptors and send efferent fibres to airway smooth muscle and glands in the lung and respiratory tract [10,11], which could lead to cardiorespiratory dysfunction and death. Diabetic patients with microvascular complications have been shown to develop more serious complications from infection with COVID-19 and may be predisposed to the development or worsening of neuropathy. In the recent CORONADO study, the presence of microvascular complications was independently associated with death within 7 days of admission with severe COVID-19 [12].

Diabetic polyneuropathy (DPN) affects over 50% of the diabetic population [13] and affects large and small nerve fibres [32,21,15]. Quantitative sensory testing (QST) allows quantitative evaluation of vibration, cold, warm and heat pain perception thresholds. We have previously used a simple quantitative sensory testing device called NerveCheck Master to quantify small and large nerve fibre dysfunction in patients with diabetic neuropathy [17,16].

In this preliminary report we describe the detailed neurological presentation and undertake quantitative sensory testing in the feet and face and evaluate taste and smell in 4 patients with diabetes who developed severe COVID-19 disease.

2. Patients and methods

The study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Barcelona Hospital. 35 patients were admitted and managed at the Barcelona Hospital SCIAS, Barcelona. They underwent testing with a throat swab (AllPlex 2019-nCoV Assay. Seegene) and had confirmed COVID 19 based on reverse transcription polymerase chain reaction identification of the RNA SARS-CoV-2, 3 specific regions, E gene, RdRP gene and N gene. Three subjects with type 2 diabetes and one subject had type 1 diabetes underwent laboratory testing and radiologic assessment according to their clinical care needs. Subjects with communication disorders, cognitive deficits or history of pain conditions or neurological disorders before the development of COVID-19 were excluded. These patients had no prior diagnosis of diabetic neuropathy in their medical records. Informed consent was obtained from all patients. Symptoms were assessed using the short form McGill pain questionnaire. Cranial nerve involvement was assessed by evaluating the oropharyngeal reflex and for the Vernet phenomenon. Taste was evaluated using sweet (0.3 M sucrose), salty (0.15 M NaCl) and neutral (mineral water) solutions. The olfactory capacity was assessed to the aroma of coffee, perfume and acetone (C₃H₆O). Quantitative sensory testing was performed using the NerveCheck Master device incorporated into protective equipment (Fig. 1).

3. Results

Three patients with type 2 diabetes and 1 patient with type 1 diabetes developed neuropathic symptoms and were referred to neurology for further evaluation. The clinical, laboratory, COVID-19 related therapy and detailed neurological examination and QST findings in these 4 patients are presented in Tables 1 and 2. Neurological symptoms developed in each patient approximately 1 to 3 weeks after the onset of COVID-19.

3.1. Patient 1

A 57-year-old male with T2DM and psoriatic arthropathy was admitted to the hospital on 28th March 2020 with dyspnoea and asthenia over 4 days. He was diagnosed with COVID-19 pneumonia and treated with Lopinavir-Ritonavir, hydroxychloroquine, ceftriaxone, azithromycin, tocilizumab, prednisone, bemiparin and low-flow oxygen. He deteriorated clinically and radiologically and was transferred to the ICU between the 5th to 7th April and again between the 9th and
| Gender/age/diabetes duration/type of diabetes | PATIENTS | PATIENT 1 | Male/57/6/T2DM | PATIENT 2 | Male/58/37/T1DM | PATIENT 3 | Female/73/5/T2DM | PATIENT 4 | Female/73/10/T2DM |
|--------------------------------------------|----------|-----------|---------------|-----------|-----------------|-----------|-------------------|-----------|-------------------|
| SYMPTOMS | dyspnoea / asthenia | fever/ nausea/ cough/ dyspnoea | diarrhoea/ abdominal pain/ dyspnoea/ fever | fever/ cough/ dyspnoea |
| CONSOLIDATION ON CHEST X-RAY | + | + | + | + | + | + | + | + | + |
| SARS-COV-2-Rt-PCR | + (throat) | + (throat) | + (throat) | + (throat) |
| INTUBATION for O2 | + | + | + | + |
| HYDROXYCHLOROQUINE | + | + | + | + |
| AZITHROMYCIN | + | + | + | + |
| RITONABIR | + | + | + | + |
| LOPINAVIR | + | + | + | + |
| METHYLprednisolone | + | + | + | + |
| BEMIPARINA | + | + | + | + |
| NEUROLOGIC SYMPTOMS | + | + | + | + |

**LABORATORY STUDY:**

| Parameter | Value 1 | Value 2 | Value 3 | Value 4 | Value 5 |
|-----------|---------|---------|---------|---------|---------|
| Haemoglobin | 14.2 g/dL | 12.2 g/dL | 11.9 g/dL | 17.7 g/dL |
| Leucocytes | 6.6 × 10⁹/L | 6.8 × 10⁹/L | 9.7 × 10⁹/L | 6.7 × 10⁹/L |
| Lymphocytes | 500 × 10⁹/L | 600 × 10⁹/L | 700 × 10⁹/L | 700 × 10⁹/L |
| Platelets | 48 × 10⁹/L | 94 × 10⁹/L | 176 × 10⁹/L | 211 × 10⁹/L |
| D-dimer | 377 ng/mL | 535–6739 ng/mL | 951 ng/mL | 710–955 ng/mL |
| Fibrinogen | 7.9 g/L | 8.8 g/L | 7.7 g/L | 7.9 g/L |
| Random glucose | 8.9 mmol/L | 10.4 mmol/L | 9.9 mmol/L | 9.6 mmol/L |
| *HbA1c* | 8.5% | 7.9% | 7.6% | 8.2% |
| Procalcitonin | 0.08 ng/mL | ND | ND | 0.11 ng/mL |
| CRP | 0 mg/L | 171 mg/L | 4 mg/L | 97 mg/L |
| AST | 41 IU/L | 35 IU/L | 16 IU/L | 35 IU/L |
| ALT | 30 IU/L | 25 IU/L | 12 IU/L | 23 IU/L |
| Urea | 5.8 mmol/L | 11.5 mmol/L | 8.8 mmol/L | 17.1 mmol/L |
| Creatinine | 78 mmol/L | 91 mmol/L | 122 mmol/L | 198 mmol/L |
| Sodium | 152 mmol/L | 136 mmol/L | 128 mmol/L | 136 mmol/L |
| Potassium | 4.3 mmol/L | 3.9 mmol/L | 4.0 mmol/L | 3.7 mmol/L |
| Ferritin | 1744 ng/mL | 735 ng/mL | 235 ng/mL | 930 ng/mL |
| NT proBNP | ND | ND | ND | 3076 pg/mL |
| Troponin I | 31.2 pg/mL | 28.3 pg/mL | 38.8 pg/mL | 74.7 pg/mL |
| Interleukin-6 | ND | 111.2 pg/mL | 48.6 pg/mL | ND |
| Gamma Glutamyl Transferase | 59 IU/L | 35 IU/L | 25 IU/L | 47 IU/L |
| Alkaline Phosphatase | ND | 46 IU/L | 124 IU/L | ND |
| Lactate Dehydrogenase | 220 IU/L | 319 IU/L | 200 IU/L | 276 IU/L |
| Creatine Phosphokinase | ND | 55 IU/L | 17 IU/L | ND |

ND: Not done, Present: +, CRP: C-reactive protein, ALT: Alanine Transaminase, AST: Aspartate Aminotransferase.

*HbA1c prior to hospitalization.
13th of April for non-invasive mechanical ventilation (NIMV) with positive end expiratory pressure (PEEP). On 14th April thoracic CT-angiography showed the presence of right lower lobar artery pulmonary thromboembolism and upper lobe ground glass opacities with a focus of “crazy-paving”. With further deterioration he was transferred to the ICU on 19th April for non-invasive mechanical ventilation and PEEP. On 26th April he recovered to return to the medical ward and 45 days after admission he was discharged from hospital to home (Table 1).

The patient reported numbness but no pain in the feet. The patellar and Achilles deep tendon reflexes were normal with a bilateral flexor plantar response. On the feet, VPT and HPT were abnormal and CPT was normal. On the face HPT was normal. Taste was absent for sweet and salt, smell was present for acetone, perfume and coffee. There was no evidence of the Vernet phenomenon and the oropharyngeal reflex was absent (Table 2).

### 3.2. Patient 2

A 68-year-old male with T1DM developed fever, nausea and a cough with dyspnoea and weakness on March 26th, 2020. On April 9th (day 14) he was admitted to hospital with hypoxemia, diagnosed with COVID-19 pneumonia and treated with Lopinavir-Ritonavir, hydroxychloroquine, ceftriaxone, azithromycin and on day 3 of admission, tocilizumab. On April 13th (day 18) he was admitted to the ICU to receive NIMV (CPAP) and steroids. After 6 days in ICU, he returned to the ward and was discharged from hospital to home on May 8th (day 43). Serial blood tests showed an IL-6 increased from 111.20 pg/mL to 424 pg/ml on day 16 with an increase in the

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**Table 2 – Neurologic tests and QST results.**

| Patient | Patient 2 | Patient 3 | Patient 4 |
|---------|-----------|-----------|-----------|
| McGill Pain Questionnaire | Numbness | + | + | + |
| Pain | – | + | – | – |
| Left leg | – | – | – | – |
| Deep Tendon Reflexes | Patellar | + | + | + | + |
| Achilles | – | – | – | – |
| Right leg | – | – | – | – |
| Patellar | + | + | + | + |
| Achilles | + | + | + | – |
| Taste | Sweet | – | + | – | – |
| Salt | – | + | – | – |
| Smell | Perfume | + | – | – | – |
| Coffee | + | – | – | – |
| Acetone | + | – | – | + |
| QST | Left foot | VPT= (N 8-12) (ABN 7-0) | 3 ABN | 0 ABN | 0 ABN | 1 ABN |
| CPT= (N 3-6) (ABN 0-2) | 5 N | 0 ABN | 0 ABN | 6 N |
| WPT= (N 3-6) (ABN 0-2) | 3 N | 0 ABN | 0 ABN | 0 ABN |
| HPT (1 °C/sec) | ABN HIGH | ABN HIGH | ABN HIGH | ABN HIGH |
| Hyperalgesia 32–35.9 °C | Normal 36–45.9 °C | Normal Moderate 46–46.9 °C | Normal Borderline 47–48.9 °C | Abnormal High 49–49.7 °C |
| Right foot | VPT=(N 8-12) (ABN 7-0) | 0 ABN | 1 ABN | 0 ABN | 3 ABN |
| CPT=(N 3-6) (ABN 0-2) | 6 N | 0 ABN | 0 ABN | 2 ABN |
| WPT=(N 3-6) (ABN 0-2) | 0 ABN | 3 N | 0 ABN | 0 ABN |
| HPT (1 °C/sec) | ABN HIGH | ABN | ABN HIGH | ABN HIGH |
| Hyperalgesia 32–35.9 °C | Normal 36–45.9 °C | Normal Moderate 46–46.9 °C | Abnormal 47–48.9 °C | Abnormal High 49–49.7 °C |
| QST | Face | NORMAL | ABN | NORMAL | ABN |
| HPT (1 °C/sec) | Hyperalgesia 32–35.9 °C | Normal 36–45.9 °C | Normal Moderate 46–46.9 °C | Abnormal 47–48.9 °C | Abnormal High 49–49.7 °C |
| Oropharyngeal Reflex | – | – | + | + | + |
| Vernet phenomenon | + | + | + | + |

QST: Quantitative sensory testing, VPT: Vibration Perception Threshold, CPT: Cold Perception Threshold, WPT: Warm Perception Threshold, HPT: Heat Perception Threshold, ABN: Abnormal, N: Normal, Present: +, Absent.
A 73-year-old male with T2DM, hypertension, ischemic heart function which allowed oxygen withdrawal after 10 days. He was discharged home from the hospital on day 56.

On day 24 technical problems with CPAP resulted in worsening respiratory failure and his D dimer was normalized and he was transferred to the ward on day 21.

Longitudinal admission for COVID-19 pneumonia. All four patients had distal numbness in the lower extremities with preserved deep tendon reflexes in three. In the case series from Wuhan, only 2.3% reported neuropathic pain, but this was 4-fold greater in those with more severe illness [1]. There is clearly a need for more precise and detailed quantification of neuropathic deficits associated with COVID-19 [18]. Indeed, a recent systematic review on behalf of the Infectious Disease Panel of the European Academy of Neurology concluded that there was a need for more careful clinical, diagnostic and epidemiological studies to characterize the manifestations and burden of neurological disease caused by SARS-CoV-2 [19].

We now show a marked abnormality in vibration, thermal and heat pain thresholds in the feet of all patients who developed neuropathic symptoms with severe COVID-19. Although, none of the patients had a history of either symptoms or signs of neuropathy in their medical records prior to hospital admission for COVID-19 infection; neuropathy is often poorly assessed [20,21,15], especially in those with T2DM [22,23]. Indeed, our studies show that the diagnosis of painful diabetic neuropathy [40] and diabetic neuropathy [25] may be missed in approximately 80% of patients.

Multicentre studies using QST in subjects with neuropathic symptoms have identified 3 subgroups: thermal mechanical sensory loss, thermal hyperalgesia and loss of thermal sensation combined with mechanical hyperalgesia [27]. The stratification of these patients according to the sensory phenotype based on the QST profile may allow precision in the selection of treatment to relieve symptoms [28].

Neuropathy and abnormalities in QST could developed or worsen following COVID-19 infection and prolonged stay in ICU with hypoxia and inflammation as well as hyperglycemia exacerbated by high doses of methylprednisolone [30].

We also show elevated heat pain thresholds in the trigeminal sensory distribution on the face in two out of four patients. Indeed, a case of bifacial weakness with paresthesia, without ataxia or other cranial neuropathies has been temporally associated with antecedent COVID-19 [29]. Furthermore, whilst taste was relatively preserved, the sense of smell to irritant and non-irritant stimuli was reduced from presentation until hospital discharge in three out of four patients. We also report an abnormal oropharyngeal gag reflex in two patients, although the Vernet phenomenon was normal in all patients. A recent case report has described a 70-year-old male who developed dysphagia and aspiration pneumonia during recov-
tery from severe COVID-19. Examination revealed altered sense of taste and an absent gag reflex and videoendoscopic, fluorography and high-resolution manometry revealed impaired pharyngolaryngeal sensation and mesopharyngeal contractile dysfunction indicative of glossopharyngeal and vagal neuropathy [31]. Corneal confocal microscopy (CCM) is a non-invasive ophthalmic technique that rapidly images corneal nerve fibres and has been used to quantify neurodegeneration in a range of peripheral and central neurodegenerative diseases [24], especially diabetic neuropathy [33,34]. We and others have also used CCM to identify corneal nerve fibre loss in patients with burning mouth syndrome [35] and Parkinson’s disease [36,37], multiple sclerosis [39,38] and dementia [40]. CCM may therefore be particularly useful for identifying neurodegeneration in patients with COVID-19.

In conclusion a proportion of patients with diabetes and severe COVID-19 may develop or show worsening of peripheral neuropathy characterized by neuropathic symptoms and small and large fibre dysfunction in the feet and face with a loss of smell. Quantitative sensory testing using NerveCheck Master incorporated into protective equipment appears to be a fast and simple procedure to objectively quantify and characterize the type and distribution of these sensory deficits. We acknowledge that lack of a history of diabetic neuropathy and normal deep tendon reflexes cannot exclude prior diabetic neuropathy. Longitudinal cohort studies using objective measures of neuropathy including QST and CCM may provide a better understanding of the development and progression of COVID 19 related neuropathy in patients with and without diabetes.

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Author contributions

A.O. researched data and wrote the manuscript. S.O and M.B. O. designed and created the NerveCheck. L.O., L.M., A.T., D.C., S.M., M.P., Y.M., M.P., A.D. researched data. R.A.M reviewed the manuscript. A.O. leads the study and edited the manuscript and is the guarantor of this work.

Conflicts of Interest

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to financial contributions to this work. Phi Med Europe S.L. provided the NerveCheck device. S. Odriozola, M.B. Odriozola and A. Odriozola are the owners and inventors of the NerveCheck.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

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