



Guillain-Barre syndrome associated with COVID-19 infection: A case series

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Abstract

In this communication, we reported a series of six patients presented with Guillain-Barré syndrome that associated with COVID-19 infection, which was confirmed with RT-PCR. Here we discuss the laboratory investigation and case management, as well as clinical presentation and outcome of each case. The current report demonstrated the first case series of COVID-19-associated GBS-cases in Sudan.

KEYWORDS

ascending paraesthesia, COVID-19, Guillain-Barre syndrome, infectious disease, neurological manifestation, neurology, Sudan

1 | INTRODUCTION

The current COVID-19 pandemic that caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

has initially started as a local outbreaks of pneumonia like illness in Wuhan, China in December 2019, soon later developed into a global pandemic in a severe gap of knowledge about the disease pathology, clinical presentation,

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transmission, prevention, and control.¹ First cases of COVID-19 in Sudan were confirmed between February and March 2020,² and with the next few months, Sudan became one of the worst African countries hit by COVID-19 pandemic.³ Furthermore, due to the limited resources, fragile healthcare system, and low coverage of COVID-19 vaccine in Sudan, people have suffered from devastating health, socioeconomic, and professional impacts of the pandemic.^{4–6} These limitations are further indicated by the growing epidemics and outbreaks of tropical diseases including malaria and cholera as well as the spread of invasive diseases vectors.^{7–12}

During the pandemic of corona virus disease several neurological manifestations have been reported.^{13,14} However, a few cases with the occurrence of Guillain-Barre syndrome and COVID-19 have been reported.^{15–17} Here, in this communication we report a series of six cases of Guillain-Barre syndrome associated with COVID-19 infection. Additionally, considering the growing burden of zoonotic viral infections in Sudan.^{10,11} Therefore, these cases were screened by ELIZA to exclude infection with other viruses involved in neurological syndromes that are prevalent in Sudan.¹⁸ Patients were seronegative for major viruses including HIV, Hepatitis E virus (HEV), human papillomavirus (HPV), and major human arboviruses such as chikungunya (CHIK), Crimean-Congo hemorrhagic fever (CCHF), dengue (DEN), Rift Valley fever (RVF), West Nile (WNV), and Zika (ZIKV) viruses.^{18–24}

Cases were presented at the outpatient clinic at the Royal Care hospital in Khartoum. Following the presentation of the first case an ethical approval was obtained from the research ethics committee (Institutional Review Board). Then, an informed consent and permission for publishing was obtained from patients.

2 | CASE REPORT

2.1 | Description of the first case

A 55-year-old man arrived at the emergency room (ER) complaining of distal ascending paraesthesia (to the elbow and knee) and he was unable to walk without assistance. Twenty-four hours prior to admission, he experienced lower limb weakness, numbness, and tingling sensation in hands and feet. Neurological examinations revealed mild lower limb paraesthesia (Medical Research Council Score (MRCS) 5/5 at upper limbs and 1/5 at lower limbs), mild hypoesthesia (reduced sensation to pinprick distal to the ankle joint), and generalized areflexia with down going plantar reflex. Two weeks before onset of the neurological complaints, he had fatigue,odynophagia, and a low-grade

fever. The Real time reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 using nasopharyngeal (NP) swab performed at admission was positive. Nerve conduction studies (NCS) showed a primary demyelinating pattern in accordance with Guillain-Barré syndrome (GBS) criteria. Intravenous immunoglobulin (IVIG) (0.4 g/kg/day for 5 days) was initiated immediately. Ten days after the treatment, the patient has full recovered (Table 1).

2.2 | Description of the second case

A 43-year-old, known epileptic woman admitted to the ER because of ascending paraesthesia of distal extremities (to the elbow and knee) and sudden weakness of distal lower extremities. Twenty-four hours prior to admission she experienced weakness in her left leg only, numbness, and tingling sensation in her hands and feet. A neurological examination showed generalized areflexia with down going plantar. A MRCS was 5/5 at upper limbs and 3/5 at lower limbs. Seventeen days ago, she had headache, myalgia, and fever. The RT-PCR for SARS-CoV-2 using NP was positive. NCS showed a demyelinating pattern in accordance with GBS criteria. IVIG (0.4 g/kg/day for 5 days) were initiated immediately after symptoms onset and clinical outcome improved 5 days after treatment. Paraesthesia started to subside and she started regaining power (Table 1).

2.3 | Description of the third case

A 55-year-old obese female with diabetes and hypertension arrived at the emergency room in a wheelchair unable to walk, she complained of back pain and paraesthesia in her lower limbs. Twenty-four hours prior to admission, she experienced heaviness in her legs and could only walk with assistance, the weakness got worse throughout the day until she became unable to walk at all. On examination, the MRCS was 0/5 at upper limbs and 0/5 at lower limbs. She had generalized areflexia with down going plantar reflex. Two days before the neurological onset, she had a low-grade fever, dry cough, andodynophagia. At the admission to the hospital, a CT scan of the thorax revealed basilar ground glass appearance. Blood profile showed leukopenia, and increased ESR and CRP. NCS showed a demyelinating pattern in accordance with GBS criteria. RT-PCR for SARS-CoV-2 using NP was positive. The first cycle of IVIG (0.4 g/kg/day for 5 days) was administered and improvement of muscle weakness was observed on day five. The patient was later able to walk with assistance (Table 1).

TABLE 1 Demographical and clinical characterization of our patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age/Gender	55/male	43/male	55/female	58/female	41/females	83/female
Comorbidities	None	None	Type 2 diabetes, hypertensive, obese.	Rheumatoid arthritis for 2 years, she took NSAIDs and steroids for a total of 2 months.	Type 2 diabetes, hypertension, obese.	Type 2 diabetes.
Symptoms of COVID-19	Fatigue, Malaise, sore throat, cough, low grade fever	Headache, myalgia, fever	Low grade fever, dry cough, soreness in throat	Productive cough (whitish sputum), malaise, headache & diarrhea	Denied respiratory, fatigue for a week	Dyspnea, cough,
Chest X-ray/CT			Chest CT-scan showed basilar ground glass appearance	CT-thorax revealed ground glass appearance.	CT-thorax ground glass appearance	CT-thorax revealed ground glass appearance.
Initial symptoms	Paresthesia, weakness,	Paresthesia, weakness	Paresthesia, weakness, back pain	Paresthesia, weakness, muscle pain	Weakness, Back pain	Paresthesia, weakness,
Clinical signs	Areflexia, Paraparesis, reduced sensation to pinprick	Areflexia, Paraparesis	Areflexia, quadriplegia	Areflexia, paraparesis	Areflexia, quadreplegia	Areflexia, paraplegia
Respiratory failure				Yes, diaphragmatic paralysis and was put on a ventilator.		
Onset of Neurological syndrome	14 days post COVID-19 symptoms	17 days post COVID-19 Symptoms	2 days post COVID-19 symptoms	4 days post COVID-19 symptoms	7 days	3 days
NCS	AIDP	AIDP	AIDP	No nerve conduction study was done because of lack of staff	AIDP	AIDP
Serum studies			Leukopenia, ESR, and CRP increased.	leukopenia, high c-reactive protein (40 mg/L),	positive D-dimer, ferritinopathy, severe leukopenia and lymphopenia	leukopenia
Treatment	IVIG (0.4 g/kg/day for 5 days) Paracetamol infusion	IVIG (0.4 g/kg/day for 5 days) Paracetamol infusion	IVIG (0.4 g/kg/day for 5 days) Paracetamol infusion	IVIG (0.4 g/kg/day for 5 days) Paracetamol infusion, Levofloxacin, Meropenem	IVIG (0.4 g/kg/day for 5 days), Paracetamol infusion	IVIG (0.4 g/kg/day for 5 days), Azithromycin (500 mg daily for 3 days), clexane
Clinical Outcome	He recovered 10 days after neurological symptoms	He recovered 5 days after receiving medication.	She had improvement with residual weakness on the fourth day	9 days after being put on the ventilator, 13 days after presentation. The patient passed away.	She responded, upper limbs and lower limbs became better 3/5, persisting areflexia. 2 to 3 days after presentation.	3 days after presentation.

Note: All patients were seronegative for HIV, HEV, HPV, CHIK, CCHF, DEN, RVF, WNV, and ZIKV viruses. All patient were positive for NP swab for SARS-CoV-2 with RT-PCR

Abbreviations: AIDP, Acute inflammatory demyelinating polyneuropathy; CSF, Cerebrospinal fluid; CT, Computed tomography; ER, emergency room; IVIG, intravenous immune globulin; GBS, Guillain-Barré syndrome; MRCS, Medical Research Council Score; NCS, Nerve conduction studies; NP, nasopharyngeal; RT-PCR, Real Time- polymerase chain reaction.

2.4 | Description of the fourth case

A 58-year old female patient presented on April 26th with a productive cough (whitish sputum), fatigue, headache, and diarrhea. The patient has a past medical history of Rheumatoid Arthritis for two-years after which she took NSAIDs and steroids for 2 months consecutively. Laboratory investigations revealed low white blood cells-leukopenia and a positive ICT test for typhoid. After taking ciprofloxacin, she started taking cefixime as the ciprofloxacin caused her fatigue. Later that day she started experiencing pins-and-needles like pain in her upper and lower limbs, along with severe muscle pain. On Wednesday, April 29th, she presented with lower limb weakness. Neurological examinations showed areflexia, upgoing plantar reflex, and a muscle power of 2/5 in all four limbs. The day after, her plantar reflex was mute (neither up going nor down going). She was given B12 (dose) and Gabapentin (dose) till Friday, May 1st. On that day, May 1st, investigations showed a high C-reactive protein (40 mg/L). On Saturday May 2nd, after meeting up with a specialist, she was diagnosed with GBS. Lumbar puncture showed high proteins (6 g/dL, no cells), normal CSF sugar, no nerve conduction study was done because of lack resources during the presentation. A negative urine culture was obtained following an observation of a mute plantar reflex. The initial result of COVID-19 diagnosis was suspected and a CT-thorax revealed ground glass appearance. IVIG (0.4 g/kg/day for 5 days) was then administered at home. On that same day, she started to experience extreme pain in the thigh. On Sunday May 3rd, she developed shortness of breath, oxygen saturation of 85% in room air and 92%–94% with oxygen (nasal cannula), a NP swab was taken and RT-PCR results came back positive for COVID-19. She was given Levofloxacin and Meropenem, and taken to the isolation center for treatment. On May 4th she developed diaphragmatic paralysis, high shooting blood pressure, hand weakness, and anxiety, she was then put on mechanical ventilation through an endo-tracheal tube. Unfortunately, the patient has passed away on May 13th (Table 1).

2.5 | Description of the fifth case

A 41-year-old obese female with diabetes and hypertension arrived at the emergency room complaining of lower limb weakness and back pain. The weakness progressed to the upper limbs within 24h. In the previous 7 days she experienced fatigue which she thought was a result of fasting Ramadan but had denied any flu-like symptoms. Neurological examinations showed generalized areflexia and down going plantar reflex. MRCS was 0/5 at upper limbs and 0/5 at lower limbs. A CT scan of the thorax revealed

showed bi-basilar consolidation and patchy peripheral ground-glass opacities in keeping with classic COVID-19. Her NP swab was positive for SARS Cov-2. The blood tests revealed leucopenia and CSF showed high protein without cells. The EMG, on the second day after admission, showed a demyelinating pattern. The patient received IVIG (0.4 g/kg/day for 5 days), and Paracetamol infusion for the back pain. She responded well after 3 days. Upper and lower limbs showed an improved power grade (3/5) (Table 1).

2.6 | Description of the sixth case

An 83-year-old female with diabetes, who experienced dry cough and dyspnea, started experiencing paresthesia in both hands and feet which started 3 days after her flu symptoms. Two days later she started experiencing heaviness in both lower limbs and difficulty in walking. Twenty-four hours later she was unable to walk and she was admitted to the neurology ward. Neurological Examination showed paraplegia and areflexia. CSF findings showed high protein. Chest CT-thorax revealed ground glass appearance. NP swab resulted positive for SARS-Cov-2. Blood tests showed leucopenia and the EMG, showed a demyelinating pattern. An IVIG standard protocol was started. The treatment resulted in motor improvement 3 days later, with paresthesia still persisting (Table 1).

3 | DISCUSSION

Several neurological manifestation were reported among patients with COVID-19, ranged from headache,²⁵ dizziness, confusion to more severe manifestation such as encephalopathy, acute disseminated encephalomyelitis, and GBS.^{14,25,26}

GBS is considered as a neuroinflammatory disease with a low global incidence between 1 and 2% per 100,000 individuals.²⁷ There are many etiological agents for GBS including viral and bacterial infection predispose to the development of GBS; however till date the exact mechanisms by which the destruction of the nerve tissues occur have not been demonstrated yet.²⁸ GBS is considered as the most common cause of acute flaccid paralysis and diagnosed by complete patient history, neurological examination, electrophysiological test, and CSF analysis. In Sudan; the diagnosis of GBS is mainly clinically due to the limited resources and diagnostic capacity in the country. Unfortunately, this imply that many other cases of GBS might have been missed due to the lack of experienced physicians in the different hospital during patients' presentation.

This study reported a series of six cases of typical GBS preceded by classic signs and symptoms of biologically

confirmed COVID-19, who were studied in Khartoum at Royal Care Hospital, Sudan, between April and July 2020. Five of the patients in this series had a positive NP swab for SARS-CoV-2 at the onset of the neurologic syndrome, and one had a negative NP swab but subsequently had a positive NP swab when the test was repeated with a new NP 3 days later.

The first symptoms of GBS in our case series were lower-limb weakness and paresthesia in the five patients and weakness with no paresthesia in one patient. Additionally, three patients presented with muscle pain, two of which had back pain. Generalized, flaccid paraparesis, or tetraplegia evolved over a period of 1–2 days in all patients; one received mechanical ventilation. The interval between the onset of symptoms of COVID-19 and the first symptoms of GBS ranged from 2 to 17 days, which is almost 150% the global average delay between COVID-19 infection and GBS manifestation.²⁹ None of the patients had dysautonomic features and four patients had leucopenia.³⁰ Five patients received a nerve conduction study, and all were generally consistent with the demyelinating variant of Guillain-Barré syndrome (AIDP).^{29,30} All patients were treated with intravenous immune globulin (IVIG).³⁰ After treatment, five patients showed improvement, one patient passed away. Although in our study, no patient needed intensive care compared to 37%, however the case fatality rate among our patients is high 17% compared to 6% globally.²⁹ This could be attributed to the lack of identifying high proportion of COVID-19-associated GBS cases due to the delay in GBS manifestation after the viral clearance.²⁹ This urges for further investigation to estimate the actual burden of COVID-19-associated GBS cases. Particularly in countries like Sudan, where heavy burden of wide range of viral infections with overlapping symptoms and involvement in GBS development existed.

4 | CONCLUSION

Based on this series of cases; it is not clear whether the infection preceded the GBS, or whether the infection is concomitant or considered a casualty in this group of patients. Furthermore, as GBS is a rare condition and COVID-19 pandemic is still continuing, therefore our report is of high important as it highlights the potential association and urge for further studies to investigate it.

The current report demonstrates the first case series of the GBS occurrence in association with COVID-19 infection in Sudan. We recommended a continuous monitoring of all COVID-19 patients with particular attention to the potential presentation of any neurological syndromes. A wider study with larger sample size of patients might be warrant to generate valuable

information useful for patients' healthcare particularly in settings with poor-resources like Sudan where diagnostic capacity is limited.

AUTHOR CONTRIBUTIONS

Ayman Ahmed: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Rahba El-Amin:** Formal analysis; investigation; methodology; writing – original draft; writing – review and editing. **Ahmed Musa:** Investigation; methodology; validation; visualization; writing – original draft. **Muaz Elsayed:** Investigation; methodology; writing – review and editing. **Lamis Fahal:** Investigation; methodology; writing – review and editing. **Eiman Siddig Ahmed:** Investigation. **Yousif Ali:** Investigation; methodology; writing – review and editing. **Ipyn Eric Nebie:** Visualization; writing – original draft; writing – review and editing. **Nouh Mohamed:** Investigation; methodology; writing – review and editing. **Jakob Zinsstag:** Visualization; writing – original draft; writing – review and editing. **Emmanuel Edwar Siddig:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing. **Dr. SARAH MISBAH EL-SADIG:** Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; resources; software; supervision; validation; visualization; writing – original draft; writing – review and editing.

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None.

CONFLICTS OF INTEREST STATEMENT

The author reports no conflicts of interest in this work.

DATA AVAILABILITY STATEMENT

All data are available within the draft.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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