Submitted: 27 September, 2023 Accepted: 06 February, 2024 Published: 08 August, 2024 DOI:10.22514/sv.2024.090

Open Access
Signa Vitae

CASE REPORT

Guillain-Barre syndrome after snakebite: a case report and systematic review

Mensure Yımaz Çakırgöz[1,*], Murat Aksun[1], Damlanur Üstün[1], Özgün Yılmaz[1], Mert Akan[2]

[1]Intensive Care Unit, Department of Anesthesiology and Reanimation, Izmir Katip Celebi University Atatürk Education and Research Hospital, 35360 Izmir, Turkey
[2]Intensive Care Unit, Department of Anesthesiology and Reanimation, Izmir Acıbadem Kent Hospital, 35630 Izmir, Turkey

***Correspondence**
mensure.cakirgoz@sbu.edu.tr
(Mensure Yılmaz Çakırgöz)

Abstract

Guillain-Barré Syndrome (GBS) is a polyneuropathy characterized by acute-onset and immune-mediated processes, triggered by various factors. The occurence of GBS in connection with snakebites is rare. In this report, we present a rare clinical case with neuro-muscular and hematological complications following a snakebite, leading to flask quadriplegia on the 14th day during intensive care follow-up. Cerebrospinal fluid (CSF) analysis indicated albumin-cytological dissociation, and Electromyography (EMG) revealed findings consistent with acute motor axonal neuropathy, resulting in a diagnosis of GBS. After undergoing plasmapheresis once, the patient swiftly developed refractory septic shock, leading to a fatal outcome. In this study, we report a GBS case as a conseqeunce of snakebite together with a systematic review of the medical literature on the development of GBS after snakebite. Although current case reports and findings have broadened the scope of etiologic hypotheses for GBS including snake envenomation, further studies are needed to confirm the association between GBS following snakebite.

Keywords

Guillain-Barre syndrome; Snakebite; Acute motor axonal neuropathy

1. Introduction

Guillain-Barré Syndrome (GBS) is a well-known, treatable acute-onset immune-mediated polyneuropathy. It is characterised by bilateral, symmetric, progressive, ascending flaccid paralysis. Around 70% of cases are associated with events such as infections, surgeries, or vaccinations, typically manifesting 2–4 weeks after the triggering incident. The worldwide annual incidence is approximately 0.5–2 per 100,000 individuals [1–4]. The development of GBS following a snakebite is rare [3–9]. Including our case, we encountered only 12, one being a pediatric one, reported cases of GBS development following snakebite in the literature review [5–14].

However, in these cases, polyneuropathy may be considered a neuro-muscular junction (NMJ) disorder, observed due to delayed envenomation from the snakebite. Therefore, clinical suspicion and careful neurological evaluation are necessary for a GBS diagnosis and patients can achieve near-complete recovery with early diagnosis and appropriate treatment. Thus, recognising this unusual complication following a snakebite holds significant epidemiological, therapeutic, and prognostic importance.

In this report, we present a rare clinical case that manifested with neuro-muscular and hematological complications following a snakebite and was diagnosed as GBS. Additionally, a systematic review of the literature to elucidate and compare clinical and prognostic information regarding the development of GBS following snakebite is also presented in this study.

2. Material and methods

In this study, medical records of GBS patients who were admitted to the Intensive Care Units of Health Sciences University Tepecik Training and Research Hospital and IKCU Atatürk Training and Research Hospital following a snakebite within the last ten years were retrospectively reviewed, we present a case report of one patient meeting the criteria for this case definition.

2.1 Case report

A 24-year-old female patient presented to our hospital's emergency department with complaints of sudden onset of nosebleed, headache, and loss of consciousness while working in a field. The patient was intubated in the emergency department due to status epilepticus following consecutive generalised tonic-clonic seizures. Brain computed tomography (CT) was normal. The patient was admitted to the intensive care unit with high-dose vasopressor support. Upon admission to the intensive care unit, the patient was sedated, had isochoric pupils, and exhibited bilateral pupil reflexes. No pathological reflexes were observed. The medical team examined the patient for any signs of snake, tick, or scorpion bites. However, no distinct bite marks were identified, given the widespread mucosal bleeding and petechiae. Additionally, there were no

witnesses to a snakebite. Due to the absence of any bite marks or witnesses, anti-venom therapy was not administered.

At the time of admission, the laboratory test results were as follows: Creatinine: 1.39 mg/dL (0.6–1.1 mg/dL), D-dimer: 2966 μg/L (<243 μg/L), Aspartate Aminotransferase (AST): 854 U/L (5–35 U/L), Alanine Aminotransferase (ALT): 2722 U/L (5–35 U/L), Total Bilirubin (T.Bil): 13.8 mg/dL (0.2–1.2 mg/dL), Lactate Dehydrogenase (LDH): 2675 U/L (0–145 U/L), Amylase: 109 U/L (28–100 U/L), Creatine Kinase (CK): 962 U/L (0–145 U/L), Hemoglobin: 10.3 g/dL (11–15 g/dL), Procalcitonin: 9.58 μg/L (<0.5 μg/L), INR (International Normalized Ratio): 2.79 seconds (0.8–1.2), Platelets (Plt): 42 $\times$ 10^9/L (150–400 $\times$ 10^9/L), lactate level 5.2 mmol/L, other routine hematological and biochemical analyzes were normal. Blood B12, folate, serum iron, ferritin, and transferritin levels were normal. The immunological and infectious examinations were unremarkable, including thyroid function and related antibodies, hepatitis markers, human immunodeficiency virus (HIV), cytomegalovirus (CMV), herpes simplex virus (HSV), Epstein-Barr virus (EBV), varicella zoster virus (VZV), as well as investigations for Crimean-Congo Hemorrhagic Fever, West Nile Fever and Leptospirosis. BOS, blood, tracheal and stool cultures were negative. Based on these findings, empirical antibiotic and supportive therapy was initiated.

On the 14th day of intensive care unit (ICU) admission, the need for vasopressors ceased, and hemodynamic and laboratory values returned to normal. However, the patient still required mechanical ventilation. Sedation was discontinued, and the patient's consciousness was monitored. Despite flaccid quadriparesis and generalized areflexia, the patient was alert, awake and cooperative. At this point, the widespread petechiae had decreased, and a double bite mark with ecchymosis was observed in the upper part of the right heel, which was not initially identified during the first examination (Fig. 1). The patient consulted with the neurology department. A detailed neurological examination revealed the patient was awake and cooperative, with mid-dilated pupils, weak bilateral light reflexes, facial diplegia, and flask quadriplegia (muscle strength assessed using the "Modified Research Council (MRC)" scale: 2/5 in proximal and distal muscles of upper extremities, 1/5 in proximal and distal muscles of lower extremities). The upper and lower extremities had a glove-and-stockingtype sensory deficit. Deep tendon reflexes could not be elicited in all four extremities. The fundoscopic examination was normal.

Magnetic resonance imaging of the brain and spine was performed to exclude central causes and was seen to be normal. On the 16th day of admission, lumbar puncture (LP) and EMG were conducted. The cerebrospinal fluid (CSF) appearance in the LP was clear, with normal pressure. CSF analysis showed albumin-cytological dissociation (no cells were detected, CSF protein was 90 mg/dL, CSF glucose was 88 mg/dL, and simultaneous blood glucose was 145 mg/dL). CSF culture showed no growth. EMG revealed severe motor axonal neuropathy. Considering the quadriplegia, generalised areflexia, albumin-cytological dissociation in CSF, and electrophysiological studies (EMG) findings, the patient was diagnosed with acute motor axonal neuropathy (AMAN), a variant of GBS. On the 17th day of hospitalization, the first plasmapheresis treatment was completed without any problems. However, vasopressor support had to be started because of fever that started 6 hours following plasmapheresis and hypotension unresponsive to fluid therapy. Echocardiography findings were normal. Cultures were taken considering septic shock and also broad-spectrum empiric antibiotherapy was started. There was no growth in cultures. The patient passed on the 22nd day of hospitalization due to rapidly developing refractory shock.

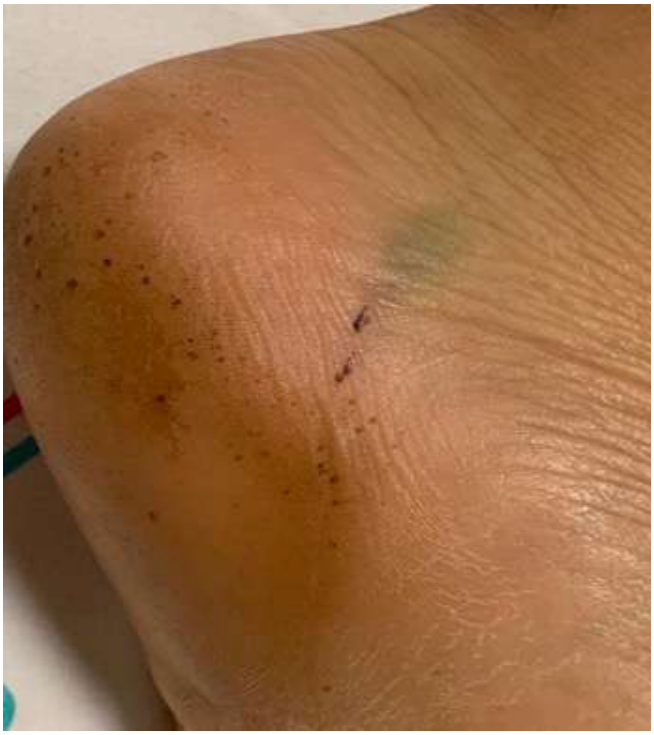


FIGURE 1. A double bite mark with ecchymosis was observed in the upper part of the right heel, which was not initially identified during the first examination.

2.2 Literature review

We conducted a systematic literature review using the keywords (GBS OR Acute inflammatory demyelinating polyneuropathy OR Acute motor axonal neuropathy) AND (snake bite OR envenomation) from PubMed, ScienceDirect and Google Scholar data bases according to the "Preferred Reporting Items for Systematic Reviews and MetaAnalyses" (PRISMA) guidelines with no time restriction for case reports or case series published in the English language. The results were reviewed and evaluated by all the authors to ensure that all data were properly extracted. DÜ and ÖY independently performed the primary data extraction. All articles were independently reviewed by two other reviewers (MYÇ and MuA). Inter-rater disagreement was minimal, and all disagreements were resolved through discussion and re-examination of the articles in consultation with MYÇ, MuA and MeA. We restricted our analysis to articles meeting the following inclusion criteria: case reports or case series with clinical, biological and electrophysiological details concerning human patients with peripheral nerve involvement following a snake bite. However, the patients with compartment syndrome or pure autonomic dysfunction, along with patients with snakebite-related neuromuscular junction or muscle involvement were

excluded. All cases developing GBS following another animal bite or sting were not considered in analysis. For each case reported, we collected (when available) the age and gender of the patient, type of snake, electrophysiological data, biological data, time duration from snakebite to clinic symptom, type of treatment and outcome (**Supplementary Table 1**).

3. Results

3.1 General findings

Including our case, we found 12 published cases of GBS following snakebite, with total of 10 studies, including 9 case reports and 1 case series [5–14] (Fig. 2). The average age of the patients (9 males and 3 females) was 33 years, ranging from 11 to 62 years. We found 12 detailed case reports of GBS after bites from snakes of various families: Elapidae (5 cases), Viperidae (2 cases) and five unidentified snakes.

The mean onset time of GBS symptoms following the snakebite was 14 days (ranging from 7 to 27 days), and the bite was localized in the upper extremity in 3 cases and in the lower extremity in 8 cases (no information in one case, P4). There were different GBS variants according to clinical (paraplegic variant in 1 case) and electrophysiological features (AMSAN in 9 cases; AMAN in 3 cases). There were quadriparesis in 11 patients (91.7%), paraplegia in 1 (8.3%), facial diplegia in 6 (50%), ophthalmoplegia in 3 (25%), autonomic dysfunction in 3 (25%), Respiratory failure in 5 (41.7%) and bulbar dysfunction (41.7%) were observed in 5 patients. Lumbar puncture was performed in 11 patients. CSF protein level was found to be significantly high (between 117–179 mg/dL) in 4 cases (33.3%), moderately high in 4 cases (between 78–90 mg/dL, the level was not reported in one case) (33.3%), yet normal in 2 cases (<45 mg/dL) (16.7%). Immediately, or within the hours following the bite, 9 patients received antivenom serum, 5 received tetanus toxoid.

3.2 Follow-up and treatment

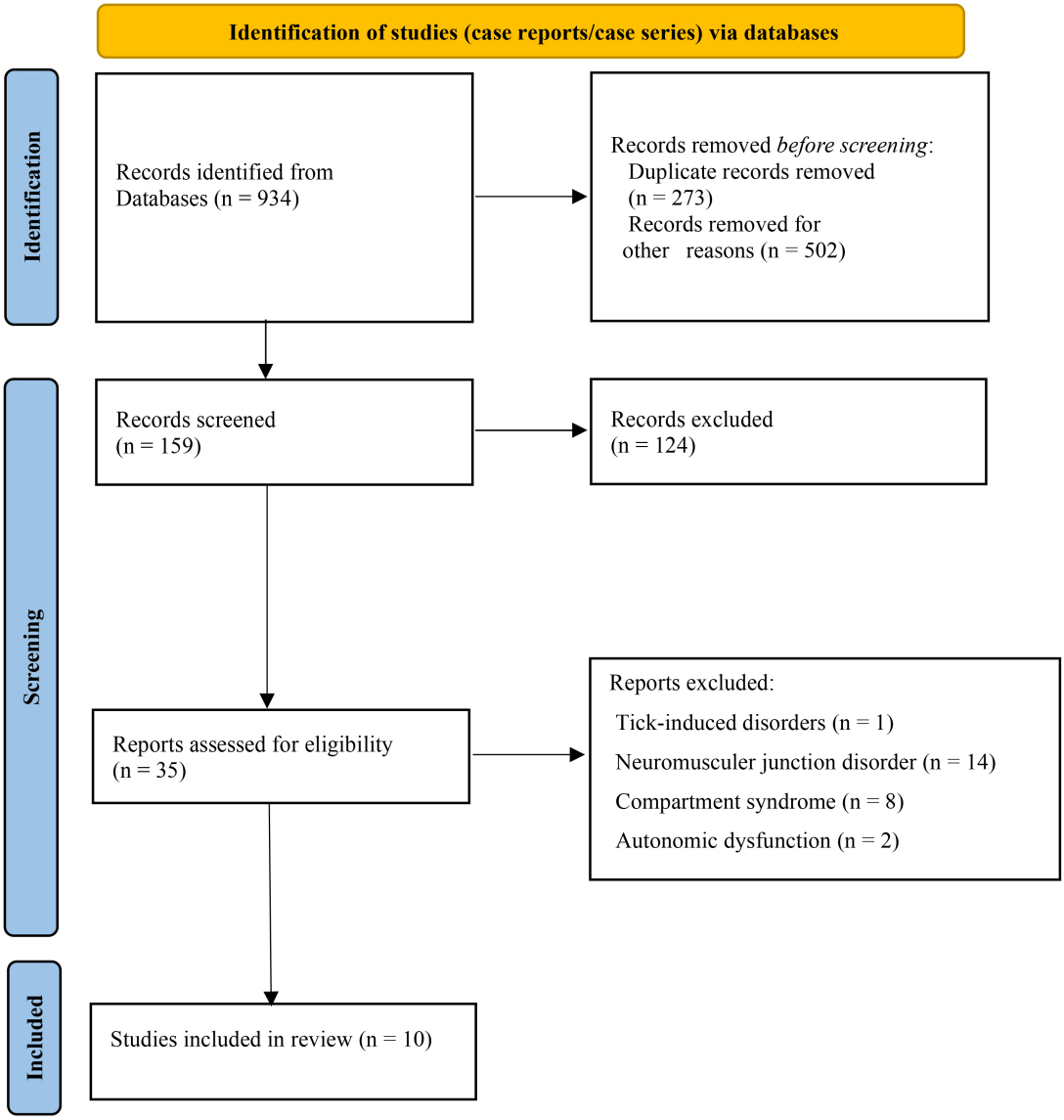
Follow-up information was available for 12 patients. While most of them recovered (91.7%), 50% of the cases showed complete (P4, P5, P7, P8, P9) or near complete (P2) recovery. Partial recovery, on the other hand, was seen in 41.7% of patients (P1, P3, P6, P10, P11), 1 patient was lost (P12).

The following immunomodulatory therapies were administered in 10 of 12 cases (83.3%; no data for P3 and P6) diagnosed with GBS after snakebite: 6 cases were treated with intravenous immunoglobulin (IVIG) (50%; P4, P5, P8, P9, P11 received a single dose, P10 received a second dose 2 months later), 3 cases were treated with plasmapheresis (30%; P2, P7, P12), 1 case was treated with a combination of plasmapheresis and corticosteroids (P1). The complete (P7) or near complete (P2) cure rate of the cases treated with plasmapheresis was 50%, while the complete (P4, P5, P8, P9) or near complete cure rate of the cases treated with IVIG was 66.7%. Antivenom treatment was administered in 9 of 12 cases (75%; P1, P2, P4, P5, P6, P8, P9, P10, P11). Though not enough to compare patients who received antivenom treatment and those who did not, the rate of complete (P4, P5, P8, P9) or near complete recovery (P2) was 56% in patients who received antivenom treatment, while it was 33.3% (P7) in patients who did not receive antivenom treatment.

4. Discussion

GBS is typically considered an immunologically mediated acute inflammatory polyneuropathy that presents with a heterogeneous clinical picture but typically results in symmetrical, flaccid, areflexic paralysis [4, 15, 16]. Today, it is a significant medical emergency and the most common cause of acute flaccid paralysis in children and adults, following the control of polio [13]. Although the exact immunopathogenic mechanism of GBS is not fully understood, it is often considered an autoimmune disease that occurs following f infections. In about 40% of patients, the etiology is unknown [3, 4, 7]. While GBS has been reported to develop after other acute events such as vaccinations and surgery, based on the available literature, including our case, we found only 12 published cases of GBS following snakebites [5–14] (**Supplementary Table 1**).

The first case of GBS associated with snakebite was reported by Chuang *et al.* [5] in 1996. The patient presented to the emergency department 4 weeks after a Formosan krait (Bungarus multicinctus) bite with areflexic progressive quadriparesis, bilateral facial paralysis, loss of consciousness and autonomic dysfunction with moderate protein elevation in CSF and severe axonal sensorimotor polyneuropathy findings on EMG and thus was diagnosed with GBS [5]. In 2010, Srivastava *et al.* [6] reported the second case of areflexic progressive quadriparesis which started 2 weeks after a snake bite of unknown species and presented to hospital 6 weeks later. The patient with sensorimotor polyneuropathy suggestive of demyelination with axonal degeneration on EMG and albuminocytologic dissociation findings in CSF was diagnosed with GBS [6]. In 2011, Neil *et al.* [7]. reported the third case of GBS who was admitted to the hospital with flaccid quadriparesis two days after Vipera aspis bite starting with progressive paresthesia and gait ataxia in four extremities 10 days after the bite, albuminocytologic dissociation in CSF, acute sensorimotor polyneuropathy on EMG (primarily suggestive of demyelination with conduction block) and a diagnosis of Guillain-Barre syndrome based on clinical findings. In 2014, Neto *et al.* [8] reported a case of a patient with areflexic flaccid quadriparesis, dysphagia, dysphonia and bilateral facial paralysis on day 14, showing onset with progressive ascending paresis 10 days after a rattlesnake (Crotalus sp.) bite. The fourth GBS case was diagnosed based on the clinical findings such as albuminocytologic dissociation in CSF, acute sensorimotor axonal polyradiculopathy on EMG (primarily suggestive of demyelination with conduction block). In 2017, Kanni *et al.* [9] reported bilateral lower extremity paralysis starting from day 15 with weakness in four extremities 10 days after snakebite. The fifth case was reported by Kanni *et al.* [9] in 2017, who was admitted to the hospital on the 20th day due to increasing weakness and radicular pain in bilateral lower extremities from the 15th day onwards with weakness in four extremities 10 days after the snake bite, acute demyelinating sensorimotor polyneuropathy accompanied by axonal degeneration on EMG and albuminocytologic dissociation in CSF,



F I G U R E 2. Search and selection criteria conducted in accordance with preferred reporting items for systematic reviews and Meta-analyses (PRISMA) criteria.

suggesting GBS (paraplegic variant. Velue *et al*. [10] in 2018 reported the sixth case of a 11-year-old girl intubated due to rapidly developing quadriparesis and respiratory distress after the snake bite (krait). Though conscious with a neurological picture improving on the 3rd day, this patient developed flaccid quadriparesis and generalized areflexia on the 6th day and was present with acute motor sensory axonal neuropathy (AMSAN) on EMG and albuminocytological dissociation findings in CSF, which led them diagnose the patient with GBS [10]. In 2019, Hameed *et al*. [11] reported the seventh GBS case who developed progressive weakness and diplopia 3 weeks after being bitten by a yellow-bellied sea snake (Hydrophis platurus). The patient presented to hospital 6 weeks after the incident with respiratory distress, fever, aspiration pneumonia, areflexic flaccid quadriparesis, dysphagia, dysphonia and his EMG revealed acute motor axonal neuropathy (AMAN) [11]. In 2021, Suresh *et al*. [12] reported, on the other hand, the 8th case pertaining to a patient who presented with neuromuscular and hematological complications after snakebite accompanied by bilateral ptosis, quadriparesis, seizure and intracranial hemorrhage, and the patient was seen to have developed generalized areflexia on the 12th day of hospitalization despite recovery of consciousness and ptosis, and EMG revealed acute sensorimotor axonal neuropathy (AMSAN) with normal CSF findings, and the patient was diagnosed with GBS. In 2023, Changadiya *et al*. [13] reported two cases of GBS diagnosed after the initial response to anti-venom treatment following elapid snakebite. In the first case, GBS was seen to have been diagnosed based on progressive areflexic flaccid quadriparesis, bilateral facial paralysis, autonomic and bulbar dysfunction on the 15th day after the snake bite and primary demyelinating motor polyneuropathy accompanied by secondary axonal changes on EMG and albuminocytologic dissociation findings in CSF. In the second case, GBS was diagnosed based on the findings such as sudden areflexic flaccid quadriparesis, bilateral facial paralysis, autonomic dysfunction and severe axonal motor polyneuropathy findings on EMG despite normal CSF findings during intensive care follow-up on the 10th day

after the snake bite defined as krait [13]. In 2023, Aradhey P *et al*. [14] reported the 11th case diagnosed as GBS based on such findings as progressive areflexic flaccid quadriparesis that started in both lower extremities on the 15th day after the first response to anti-venom treatment following the snake bite, primary demyelinating motor polyneuropathy accompanied by secondary axonal changes on EMG together with bilateral facial paralysis and albuminocytologic dissociation findings in CSF.

Snakebite is a common occurrence. While exact data are unavailable, according to the World Health Organization, there are an estimated 4.5 to 5.4 million snakebites, 1.8 to 2.7 million envenomings, and 81,000 to 138,000 deaths annually [17, 18]. Despite these significant numbers, only 11 cases of GBS following snakebites have been reported in the literature [5–14]. This suggests that the true incidence may be much higher than the literature indicates due to insufficient documentation and reporting.

There are three main toxins in snake venom: cytotoxin, hemotoxin and neurotoxin. However, snake venoms are complex combinations consisting of enzymes, polypeptides, non-enzymatic proteins, nucleotides and carbohydrates, many of which may have different toxic properties, not containing a single toxin homogeneously [14, 18–20]. Although syndromes in terms of poisoning can vary greatly among different species within a geographic region, their effects can bear several clinical similarities. However, since venom components in a species may vary seasonally, geographically and ontogenetically, the effects of a given bite from given snake species may also vary. Therefore, in cases where the bite is not observed and accurate identification of the biting species is not possible, the appearance of the wound and the clinical status can serve as the basis for diagnosing envenomation and predictive of possible snake species, though not possible to identify a particular snake species based on the effects of envenomation [19, 20]. Cytotoxic venomous snakes include vipers, rattlesnakes and some species of cobras. Pain, edema, blisters or dermonecrosis may occur in the tissue due to cytotoxicity. However, Krait bite does not cause any local reaction, making the diagnosis quite intricate [13, 18, 20]. Hematotoxic abnormalities are characteristic of Viperidae poisoning. Procoagulant toxins in hemotoxic poisons are characterized by thrombotic microangiopathy, thrombocytopenia, microangiopathic hemolytic anemia and acute kidney injury, which can be accompanied by consumption coagulopathy, which can lead to depletion of clotting factors and spontaneous bleeding. Yet, it may also be accompanied by thrombotic conditions such as myocardial infarction and stroke (may be hemorrhagic or ischemic, but ischemic strokes are more common) [14, 18–20]. Acute neuromuscular paralysis is an important cause of morbidity and mortality due to snakebite and traditionally occurs due to postsynaptic and/or presynaptic neuromuscular blockade. Neurotoxins are the main component of venom in the Elapidae family, which includes Naja and Bungarus species called cobras and kraits, respectively. While cobra venom acts mostly postsynaptic, krait venom acts mainly pre-synaptic; still, numerous snake venoms contain both pre-synaptic and post-synaptic neurotoxins [14, 18–20]. Both types of neurotoxins can cause descending, flaccid paralysis to progress into a life-threatening respiratory failure. Although the prevalence of neuromuscular paralysis varies in most case series, ptosis has been reported in 70–93% of patients, extraocular muscle weakness in 68–82%, respiratory muscle weakness in 27–87%, and mortality in 4–37%. Delay in access to intensive care and antivenom, prolonged hospitalization with mechanical ventilation and other supportive care are significant contributors to morbidity, mortality and cost of care. In addition, neurological symptoms may be observed due to accompanying clinical status such as hypotension, shock and other organ dysfunctions (acute nephrotoxicity) as well as coagulopathy (hemorrhagic or ischemic stroke) [13, 18–20].

In our case, the presence of a double tooth mark, not associated with a local reaction, in line with previous reported cases, suggested a krait bite. However, the presence of hematological findings as well as neurological findings indicated that the venom type was a mixed one. Although epilepsy and loss of consciousness were determined by normal brain CT imaging, being non brain edema related; hemorrhagic stroke or Posterior Reversible Encephalopathy Syndrome (PRES) at the time of initial admission, encephalomyelitis or ischemic stroke was determined by contrast-enhanced Magnetic resonance imaging (MRI) and LP, which could not be applied at the time of admission due to hemodynamic instability and prolonged bleeding parameters, but on the 14th day of hospitalization. Most poisons cannot cross the blood-brain barrier. However, there are a few case reports reporting effects that are likely to be directly related to central neurotoxicity, such as drowsiness, coma, and loss of brainstem reflexes, after snake bite [19, 21–23]. In this case, epilepsy and loss of consciousness may be related to neurological changes associated with the accompanying clinical picture and/or direct central neurotoxicity.

While the exact immunopathogenic mechanisms of GBS are not known, evidence suggests that it is an autoimmune disease that affects the peripheral nerves, linked to molecular mimicry and cross-reactivity between structural components of peripheral nerves (such as GM2 ganglioside, galactocerebroside) and epitopes from infectious agents or exogenous substances [3, 7, 16]. Various mechanisms, including humoral and cellular immune responses, autoantibodies, complement, activated macrophages, and lymphocytes, have been shown to play a role in the pathogenesis of GBS. More than half of GBS patients have autoantibodies against specific epitopes found in gangliosides or ganglioside complexes in the myelin sheath [16]. These autoantibodies, such as galactocerebroside and Mycoplasma pneumonia or GM2 ganglioside and cytomegalovirus (CMV) glycans, can arise through molecular mimicry. However, the relationship between specific anti-ganglioside antibody reactivities and specific disease variants (*e.g.*, anti-GM1 for pure motor type GBS and anti-GQ1b for Miller-Fisher syndrome (MFS)) is well established [3, 16]. Similarly, molecular mimicry is the possible mechanism causing damage to peripheral nerves in cases of GBS following snakebite. Likewise, in instances of GBS following snakebite, the potential mechanism leading to damage in peripheral nerves is molecular mimicry. Neil and colleagues ruled out the potential neurotoxicity of viper venom in a patient diagnosed with GBS after a snakebite by demonstrating that the venom did not contain phospholipase A2 neurotox-

ins. They also demonstrated, through Western blot analysis, cross-reactivity between glycosidic epitopes of venom proteins' and neuronal GM2 gangliosides. This proved that molecular mimicry mechanisms between venom glycoproteins and myelin components are responsible for the etiopathogenesis [7]. Another possibility is that the predominant foreign protein structure of anti-venom or tetanus vaccines, administered in most cases, might also be associated with this autoimmune phenomenon. However, in our case report and the report by Neil *et al.* [7], three patients (P3, P7, P12) did not receive anti-venom/tetanus vaccine. Furthermore, the association between GBS and vaccination is rare and controversial. Although the link between tetanus vaccination and GBS has only been documented in a few case reports, there is no substantial research to establish a causal relationship [14]. It has been noted that snake venom remains in circulation for seven days [13]. The reported case reports indicated that neurological symptoms appeared 1–12 hours following snakebite and almost completely disappeared 3–4 days later. The timing of GBS symptoms, which occurred 1 to 4 weeks after snakebite, and the evidence of cross-reactivity of venom proteins in the literature further support that the development of GBS is secondary to the venom toxin. While the existing case reports and findings have broadened the range of etiological hypotheses for GBS to include snake envenomation, more research is needed to confirm the relationship between snakebite and GBS.

GBS typically induces symmetric, ascending, progressive flaccid paralysis in the extremities, although the clinical presentation can vary. Patients may experience distal paresthesia, numbness, arm and leg pain, and back pain. Cranial nerve involvement is observed in about 50% of patients, and autonomic dysfunction accompanies the condition in about 25% of cases. The diagnosis is based on clinical criteria, as there are no diagnostic biomarkers available for most patients [3]. According to the Brighton criteria, the classic GBS diagnosis requires, at a minimum, bilateral flaccid paralysis in the extremities with the absence or reduction of deep tendon reflexes in the absence of alternative explanations. For higher diagnostic precision or to support the diagnosis in atypical variants, the presence of albumin-cytologic dissociation in cerebrospinal fluid (an increase in proteins without pleocytosis) and the evidence of neuropathy in electromyography (EMG) are required. However, cerebrospinal fluid and EMG findings can be normal in the early (first week) stages [3, 24, 25]. EMG is essential for supporting the diagnosis of Guillain-Barré syndrome and establishing the electrodiagnostic classification of demyelinating or axonal subtypes [24]. In cases of GBS following a snakebite, the clinical presentation is typically characterised by areflexic progressive, symmetric flaccid quadriplegia, with only one presenting with the paraplegic variant of GBS. Interestingly, in contrast to the literature, cranial nerve involvement (8 patients) is more common in these cases, while the frequency of autonomic dysfunction (3 patients) is similar. Three patients showed moderately elevated protein levels in the cerebrospinal fluid (CSF), while two had normal CSF findings. The variability in CSF findings is consistent with the literature. CSF examination and variables depend on the patient and the severity of the disease. This result could be related to the early timing of CSF examination in the clinical course. Seven of the 12 patients who underwent EMG exhibited axonal involvement, and five had demyelinating polyradiculoneuropathy. Therefore, it can be concluded that the immune damage following a snakebite is not specific to any GBS syndrome model, and the venom can trigger both variants of GBS.

In Guillain-Barré syndrome, the overall prognosis is good, and complete recovery is often observed. However, about 19% of patients may require long-term monitoring in the intensive care unit or mechanical ventilation support. Despite treatment, approximately 20% of patients may experience significant residual effects, and the mortality risk ranges from 5% to 17%. Poor prognostic factors include advanced age, a history of C. jejuni infection, the need for ventilation, and the axonal subtype of Guillain-Barré syndrome [3]. When reviewing case series, it is observed that, in contrast to the literature, patients diagnosed with GBS following a snakebite require more frequent intensive care unit monitoring (7 patients), while the risk of mortality (1 patient) is at similar rates. However, when excluding the patient who died from the 12 cases, it was reported that out of the remaining 11 patients, six recovered with complete (P4, P5, P7, P8, P9) or near-complete (P2). At the same time, 5 had varying degrees of neurological sequelae despite prolonged physical therapy (P1, P3, P6, P10, P11). Although there is no information about the need for intensive care and long-term follow-up after discharge, the higher risk of neurological sequelae may be associated with the frequency of axonal damage in this patient population. The age distribution among the cases with GBS developing after a snakebite is heterogeneous, and in line with the literature, the proportion of males was higher.

Guillain-Barré syndrome (GBS) is a relatively common neurological emergency that requires early diagnosis for safe management and appropriate treatment. Particularly in cases of classic GBS, a delay of more than five days in diagnosis has been reported to negatively affect inpatient mortality [15]. Therefore, based on the clinical presentation in the case series, especially in regions where snakebites are common, the public and individuals seeking medical attention should be informed about the possibility of developing new progressive flaccid paralysis after a snakebite. They should be observed for several weeks, and if symptoms are present, prompt evaluation is recommended [7]. The course of the disease in Guillain-Barré syndrome has been classified into 3 phases depending on the time of onset of symptoms as acute phase (within 2 weeks of disease onset before irreversible axonal damage), progressive phase (usually 2–4 weeks after disease onset), recovery phase (usually between 4–8 weeks of disease onset) [3]. Immunomodulatory therapies constitute the mainstay of treatment, backed by studies showing that IVIG and plasma exchange have proven equally effective in improving disease outcome in the acute phase of GBS by accelerating recovery, but do not halt disease progression or alter the extent of nerve damage. Corticosteroids suppress hyperreactive autoimmunity but have no proven role [6, 26]. Both immunomodulator treatment are associated with few adverse events. Plasma exchange is associated with significant adverse effects which include hemodynamic instability, dilutional coagulopathy, hypocalcemia, septicemia, thrombosis, pneumo-

nia, complications from central venous access and allergic reactions. However, myocardial infarction, renal function impairment, hyponatremia, hemolysis and thromboembolism may rarely develop as adverse effects of IVIG [3, 4, 26]. While the culture results were negative in our patient, her probable cause of death of septic shock due to catheter-related infection caused by prolonged intensive care unit stay.

Our study has several limitations. The first is the small number of patients despite being the largest reported case series; secondly, many important details such as history, treatment and long-term follow-up results were not reported in most of these case reports, and neurological or electrophysiological findings were not reported in some of them, either, which poses another limitation in the analysis of the data. Third, in our case, as the patient had an epileptic attack following his admission to the emergency department and the intensive care period accompanied with multiple organ failure, detailed anamnesis regarding important triggers such as previous infections and vaccines could not be obtained, and anti-gangliocyte antibodies were not tested in serum and CSF.

5. Conclusion

Guillain-Barré Syndrome is an acute polyneuropathy with various etiologies. In our case report, as in the case reports reported in the literature, the emergence of GBS findings in 1 to 4 weeks after snake bite suggests that it indicates an immunopathological etiology rather than the direct effects of snake venom. However, more studies are needed to confirm the relationship between snakebite and GBS. GBS is a relatively common neurological emergency that requires early diagnosis for safe management and adequate treatment. Therefore, it is important from an epidemiological, therapeutic and prognostic perspective to observe patients for new-onset flaccid paralysis for a few weeks for the early diagnosis of this late complication that occurs following snake bite.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

MYÇ—designed the study, collected and analysed the data, critically reviewed and prepared the manuscript. MuA—designed the study. DÜ—collected and analysed the data. ÖY—collected and analysed the data. MeA—designed the study. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Health Sciences University Tepecik Training and Research Hospital Non-Interventional Research Ethics Committee Decision No. 2023/09-34. Written informed consent was obtained.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1813131436047122432/attachment/Supplementary%20material.docx.

REFERENCES

[1] Shang P, Feng J, Wu W, Zhang HL. Intensive care and treatment of severe Guillain-Barré syndrome. Frontiers in Pharmacology. 2021; 12: 608130.
[2] Çakırgöz MY, Duran E, Topuz C, Kara D, Turgut N, Türkmen ÜA, *et al*. Syndrome of inappropriate antidiuretic hormone secretion related to Guillain-Barré syndrome after laparoscopic cholecystectomy. Brazilian Journal of Anesthesiology. 2014; 64: 195–198.
[3] Shahrizaila N, Lehmann HC, Kuwabara S. Guillain-Barré syndrome. The Lancet. 2021; 397: 1214–1228.
[4] Florian IA, Lupan I, Sur L, Samasca G, Timiș TL. To be, or not to be… Guillain-Barré syndrome. Autoimmunity Reviews. 2021; 20: 102983.
[5] Chuang T, Lin S, Chan R. Guillain-Barré syndrome: an unusual complication after snake bite. Archives of Physical Medicine and Rehabilitation. 1996; 77: 729–731.
[6] Srivastava A, Taly AB, Gupta A, Moin A, Murali T. Guillain-Barré syndrome following snake bite: an unusual complication. Annals of Indian Academy of Neurology. 2010; 13: 67–68.
[7] Neil J, Choumet V, Le Coupanec A, d'Alayer J, Demeret S, Musset L. Guillain-Barre syndrome: first description of a snake envenomation aetiology. Journal of Neuroimmunology. 2012; 242: 72–77.
[8] Neto EGC. Guillain-Barré syndrome after a snakebite: case report and literature review. Brazilian Journal of Neurology and Psychiatry. 2014; 18: 253–257.
[9] Kanni Y. Guillain-Barre syndrome (paraplegic variety) following snake bite. Journal of Basic and Clinical Research. 2017; 4: 26–27.
[10] Velu GV. Guillain-Barre syndrome: an unusual complication after a snake bite in a child. University Journal of Medicine and Medical Specialities. 2018; 4: 30.
[11] Hameed S, Memon M, Khan S. Guillain-Barre syndrome following a snakebite: a case report and review of literature. Cureus. 2019; 11: e5278.
[12] Suresh BV. Guillain-Barre syndrome following snake bite? An underreported entity. IP Indian Journal of Neurosciences. 2021; 7: 181–183.
[13] Changadiya K, Anadure RK, Sreen A, Gupta S, Singh S, Mhatre R. Two unusual cases of Guillain-Barre syndrome after snake bite: the rare immune mediated complication of Elapid venom. Medical Journal Armed Forces India. 2023; 79: 321–327.
[14] Aradhey P, Gade N, Panjwani D, Kathpal J. Guillain-Barré's syndrome post snake envenomation: rare case report and literature review. Neurology India. 2023; 71: 320.
[15] Bose S, Loo LK, Rajabally YA. Causes and consequences of diagnostic delay in Guillain-Barré syndrome in a UK tertiary center. Muscle Nerve. 2022; 65: 547–552.
[16] Lleixà C, Martín-Aguilar L, Pascual-Goñi E, Franco T, Caballero M,

de Luna N, *et al*. Screening in Guillain-Barré syndrome. Journal of Neuroinflammation. 2021; 18: 251.

[17] Suhita R, Begum I, Rashid M, Chandran VP, Shastri SA, Kantamneni R, *et al*. Systematic review and meta-analysis of global prevalence of neurotoxic and hemotoxic snakebite envenomation. Eastern Mediterranean Health Journal. 2022; 28: 909–916.

[18] Huang YK, Chen YC, Liu CC, Cheng HC, Tu AT, Chang KC. Cerebral complications of snakebite envenoming: case studies. Toxins. 2022; 14: 436.

[19] Ranawaka UK, Lalloo DG, de Silva HJ. Neurotoxicity in snakebite—the limits of our knowledge. PLOS Neglected Tropical Diseases. 2013; 7: e2302.

[20] Seifert SA, Armitage JO, Sanchez EE. Snake envenomation. The New England Journal of Medicine. 2022; 386: 68–78.

[21] Prakash S, Mathew C, Bhagat S. Locked-in syndrome in snakebite. Journal of the Association of Physicians of India. 2008; 56: 121–122.

[22] Goyal JP, Shah VB. Suppression of brainstem reflexes in snakebite. Indian Pediatrics. 2009; 46: 360–361.

[23] Mathis S, Carla L, Duval F, Nadal L, Solé G, Le Masson G. Acute peripheral neuropathy following animal envenomation: a case report and systematic review. Journal of the Neurological Sciences. 2022; 442: 120448.

[24] Liang H, Cao Y, Zhong W, Ma Z, Liu J, Chen H. Miller-Fisher syndrome and Guillain-Barre syndrome overlap syndrome following inactivated COVID-19 vaccine: case report and scope review. Human Vaccines & Immunotherapeutics. 2022; 18: 2125753.

[25] Rath J, Zulehner G, Schober B, Grisold A, Krenn M, Cetin H, *et al*. Cerebrospinal fluid analysis in Guillain-Barré syndrome: value of albumin quotients. Journal of Neurology. 2021; 268: 3294–3300.

[26] Liu S, Dong C, Ubogu EE. Immunotherapy of Guillain-Barré syndrome. Human Vaccines & Immunotherapeutics. 2018; 14: 2568–2579.

How to cite this article: Mensure Yılmaz Çakırgöz, Murat Aksun, Damlanur Üstün, Özgün Yılmaz, Mert Akan. Guillain-Barre syndrome after snakebite: a case report and systematic review. Signa Vitae. 2024; 20(8):95-102. doi: 10.22514/sv.2024.090.