
CASE REPORT

Dengue Fever and Graves' Disease Complicated with Guillain-Barre' Syndrome: a Case Report

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ABSTRACT

GBS is a rare neurological autoimmune disorder in which a person's immune system mistakenly attacks part of peripheral nervous system and the network of nerves that carries signals from the brain and spinal cord to the rest of the body. GBS is not commonly found alongside Graves' disease or dengue fever. 35-year-old woman who have been previously diagnosed with Graves' disease with dengue fever and GBS. On the fifth day of treatment, she showed signs of poor respiratory function, weak neck muscle power, paralyzed and was indicated for intubation. The cerebrospinal fluid analysis showed a consistent finding of GBS of albumin cytological dissociation with an increased level of protein of 80 mg/dL, glucose 50 mg/dL, and a normal lymphocytes cell count of 4/cmm without polymorphs. She was ventilated for three days and began to receive the treatment of intravenous immunoglobulins (IVIG) of 0.4 g/kg/day for a total of five days and remarkable recovery and was extubated on day 3 of IVIG. The case study theorises those endogenous factors, such as gangliocytes and ICAM-1, as well as exogenous factors such as bacterial and viral infection, may play a part in the simultaneous presentation of GBS and Graves' disease. Antibodies that formed from these factors have an affinity to GM1 and GT1A gangliosides which are typically exposed on the plasma membrane and can cause molecular mimicry as well as cytokine stimulation which is the main feature of GBS. Furthermore, it is thought that preceding infection of dengue virus may also lead to the development of GBS. Intravenous immunoglobulin therapy shows a promising result on treating a simultaneous case of GBS presenting in patient with Graves' disease and dengue fever.

Keywords: *Guillain barre syndrome, dengue fever, graves' disease*

INTRODUCTION

Graves' disease and Guillain-Barré syndrome (GBS) are both autoimmune disorders, but the pathomechanisms are very different. Graves' disease is an autoimmune disease that affects thyroid gland, and the symptoms are a result of antibodies binding to receptors on the thyroid causing over-expression of thyroid hormone.¹

GBS is a rare neurological disorder in which a person's immune system mistakenly attacks part of the peripheral nervous system and the network of nerves that carries signals from the brain and spinal cord to the rest of the body. GBS usually starts a few days or weeks following a respiratory or gastrointestinal bacterial or viral infection.² One of the most common risk factors for GBS is infection with the bacteria *Campylobacter jejuni*, SARS-COV-2, Zika, Cytomegalovirus, or Epstein-Barr viruses. Although rare, few cases of GBS have been causally linked to serologically confirmed dengue illness in the medical literature. Etiopathogenesis of GBS following dengue is not yet fully described, but the molecular mimicry causing an immune attack on myelin and axons, and pro-inflammatory cytokines such as tumor necrosis factor (TNF), the interleukins, and complements participating in immune response are postulated as possible mechanisms.³

CASE ILLUSTRATION

A 35-year-old woman was admitted in February 2024 with a 4-day history of fever with arthralgia, myalgia, headache, and generalized malaise. She had a no difficulty in breathing and coughing. She denied recent diarrheal or respiratory illness. She was previously apparently well, but she had previous history of Graves' disease with no significant comorbidities. For 3 years she received antithyroid drug, but 1 month before being admitted to the hospital she was given radioactive iodine therapy at a dose of 5 milli curies. On examination, she was moderately ill, conscious, rational, and had normal vital parameters. Cardiovascular, respiratory, abdominal, and extremity examinations were normal. On skin examination, there were no

spontaneous petechiae, but the Rumpel Leede result was positive.

The complete blood count on admission showed a white cell count of $2.2 \times 10^6/\mu\text{L}$, Platelets of $46 \times 10^3/\mu\text{L}$, and a hematocrit of 40%. Her nonstructural protein 1 (NS1) antigen result was positive. With the compatible history, positive dengue antigen, leukopenia, and thrombocytopenia, a diagnosis of dengue fever was made. Laboratory examination of thyroid function showed free T4 0.78 ng/dL and TSHs 1.2 uIU/mL during treatment with antithyroid drug, thiamazole 5 mg a day.

On the 5th day of treatment, the patient complained of shortness of breath and a feeling of bloating in his stomach. Lung rales and ascites were found on physical examination. Limb examination revealed hypotonia and reduced power in the bilateral lower limbs. Her upper limbs were normal, but lower limb tendon reflexes were absent with reinforcement and her upper limb reflexes were diminished. All her sensory modalities were intact. Although she had a good cough reflex, her neck muscle power was reduced. A cranial nerve examination was normal. Laboratory examination results showed an increase in WBC of $12.3 \times 10^6/\mu\text{L}$ and platelets of $96 \times 10^3/\mu\text{L}$ and decrease in hematocrit of 38% and albumin 2.4 g/dL. Brain and spine MRI revealed no abnormalities. Initially, to this was thought to be thyrotoxicosis related to neuropathy. Antithyroid thiamazole was stopped, and propylthiouracil with propranolol and methylprednisolone injections were initiated, but her symptoms rapidly progressed with ascending weakness of lower extremities and deteriorated neurologically. She was having poor respiratory effort with low neck muscle power. She was electively paralyzed and intubated. Brain and spine MRI revealed no abnormalities. A cerebrospinal fluid study showed albumin cytological dissociation; protein 70 g/dL, cell count lymphocytes 5/cumm, and no polymorphs, consistent with diagnosis of GBS.

Our patient was started on intravenous immunoglobulins (IVIG) 0.4 g/kg/day (20 g in this 50 kg weighing woman). She was ventilated for

3 days, and intravenous immunoglobulins were administered for a total of 5 days. She made a remarkable recovery and was extubated on day 3 of IVIG. She was able to walk without support on discharge.

The dengue illness of our patient followed an uncomplicated course without clinical or ultrasonic evidence of hemoconcentration. The lowest thrombocytopenia noted was $22 \times 10^3/\mu\text{L}$ on the eighth day of her illness. Transaminases were significantly elevated, AST 364 U/L and ALT 240 U/L. Both dengue virus-specific immunoglobulin M (IgM) and immunoglobulin G (IgG) were positive on the ninth day of his illness. On discharge, she was fully recovered neurologically.

DISCUSSION

Dengue is an arboviral infection commonly presenting with fever, arthralgia, headache, and rashes. It is a major global public health challenge. Neurological manifestations of dengue fever are rare but have been reported in the medical literature. Guillain-Barré Syndrome, also known as GBS, is a rare neuromuscular disease that affects the peripheral nervous system.⁴

There has been a suggestion that the inflammatory cytokines produced from the dengue infection may lead to the development of GBS. It is thought that the dengue virus was able to increase the permeability of the blood-brain barrier, allowing the antibody to present itself to the cellular membranes. A case study in 2023 conducted by Lim et al., shows a patient showing signs of GBS after being previously diagnosed with Dengue Haemorrhagic Fever (DHF). The patient initially showed the typical symptoms of DHF with fever, arthralgia, and diarrhoea. The patient started to experience weakness and numbness in the lower limb after the second day of fever. The neurological examination showed a reduced muscle power distally and an absent deep tendon reflex as well as plantar reflexes.

The nerve conduction study reveals a bilateral asymmetrical mixed sensory and motor demyelinating polyneuropathy which is a

common finding in GBS. It is unlikely that the two cases coincidentally occur as the symptoms have been presented in the early phase of dengue.⁴

According to the study conducted by Global Burden of Diseases in 2019, there was an increase of prevalence of GBS between the year 1990-2019 of around 6.4% per 100,000 population. The global number of cases had risen from 90,249 in 1990 to 150,095 in 2019. GBS is seen to be more prevalent in the young and the elderly with the highest number of cases found in the 5-9-year age group. The rising prevalence was also associated with an increase in terms of GBS related disability. In Indonesia, the prevalence of GBS is found between 1 to <1.25 per 100.000 population.⁵ Patients with GBS are at risk of developing respiratory distress, cardiovascular dysfunction, as well as progressive weakness. It can occasionally occur after 1-2 days since the onset of the disease and may reach maximum severity at 2-4 weeks. The causes of death are often the result of cardiac arrest or acute respiratory distress syndrome. Symptomatic treatments, such as assisted ventilation, are needed in one quarter of the patients. Tracheostomy might be needed if there is a prolonged need for mechanical ventilation. It is necessary that most patients are admitted for observation of respiratory, autonomic, and motor function.⁶

The gold standard treatment of GBS lies in plasma exchange therapy and IV Immunoglobulin (IVIG) therapy. Immediate therapy is needed in patients with signs of respiratory distress, mobility problems, as well as reduction in vital signs. Plasma exchange allows plasma from cells to be separated from cells using filtration or centrifugation while the cells are re-infused back into the patient with GBS. Albumin is then used to maintain volume and osmotic equilibrium. IVIG is easier and safer compared to plasma exchange therapy however the efficacy between the two therapies was found to be similar. According to the American Society for Apheresis guideline for the

use of therapeutic apheresis, a therapeutic plasma volume (TPV) of 1-1,5 TPV is recommended over the course of 5-6 therapies over 10-14 days. A case study conducted by Stoian et al., reveals a significant improvement in patient with GBS undergoing four routine plasma exchange therapy with alternate doses between 0,5-1,2 TPV. Respiratory symptoms have improved after the first plasma exchange therapy.⁶

The developed of GBS alongside Graves' disease is rarely reported. A rare case study in 2019 by Majumder et.al shows a patient who develop Graves' disease alongside GBS.¹ The case study theorises those endogenous factors, such as gangliocytes and ICAM-1 as well as exogenous factor, such as bacterial and viral infection, may play a part in the simultaneous presentation of GBS and Graves' disease. Antibodies formed from these factors have an affinity to GM1 and GT1A gangliosides which are typically exposed on the plasma membrane of the peripheral nerves in the nodes of Ranvier and can cause molecular mimicry as well as cytokine stimulation which is the main feature of GBS. Simultaneously, these factors may also lead to the development of thyroid receptor antibodies (TRAb), which is the main factor in the development of Graves' disease. It is important to note, however, that the bacterial and viral infection that preceded each disease are different and more studies are needed to find a common infective ethology for both diseases.⁷

CONCLUSION

This case illustrates the importance of high clinical suspicion of GBS when a patient with Graves' disease and dengue fever infection develops GBS pattern neuropathy. Graves' disease is known to cause neuropathies, but the association between GBS and Graves' disease is less clear. Both are autoimmune disorders and can have common mechanisms or predisposing factors, but elevated thyroid hormones seem to be independently associated with nerve damage through increased oxidative stress. GBS begins suddenly and can increase

in intensity over a period of hours, days, or weeks until certain muscles cannot be used at all. Some cases of GBS are very mild and only marked by brief weakness. Others cause nearly devastating paralysis, leaving the person unable to breathe on their own. In these cases, the disorder is life-threatening, potentially interfering with breathing, blood pressure, and heart rate. The patient was treated with IVIG with clinical improvement. Fortunately, most people eventually recover from even the most severe cases of GBS. After recovery, people may continue to have some weakness.

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