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Clinical case

# Guillain-Barre syndrome as a manifestation of Cushing's disease secondary to Crooke's cells tumor

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## Abstract

**Background:** Guillain–Barré syndrome (GBS) is an inflammatory disease that affects the peripheral nervous system. Cushing's disease (CD) is the most common type of endogenous Cushing syndrome (CS). Few literature reports are available on the coexistence between both diseases. We present a patient who developed Guillain–Barré syndrome-compatible polyneuropathy as a manifestation of Cushing's disease secondary to a Crooke cell tumor.

Objective: To recognize that most cases of hypercortisolism lack typical clinical features, healthcare personnel must maintain a high level of suspicion to ensure early diagnosis.

**Case presentation:** We present the case of a 64-year-old female patient with type 2 diabetes mellitus, hypertension, major depressive disorder, and a suicide attempt in the last year, who consulted the emergency department by exacerbation of her mood disorder after a fall with traumatic brain injury without loss of consciousness. She presented symmetrical, progressive, distal to proximal progressive weakness due to Guillain-Barré syndrome. However, hypokalemia secondary to Cushing's disease caused by a pituitary adenoma was documented. Treatment with intravenous immunoglobulin and transsphenoidal surgery were carried out. Histopathological study confirmed ACTH-producing Crooke's cell adenoma. Both mobility, electrolytes, and the mood disorder improved after treatment.

**Discussion:** This case highlights a patient with nonspecific symptoms, an unusual presentation of a known pathology, and a rare etiopathological origin, making it valuable to examine and discuss.

**Conclusions:** Guillain-Barré syndromes are usually sporadic. There are few cases documenting concomitance between Cushing's and Guillain-Barré syndromes, this being the first case describing Crooke cell-type ACTH-producing pituitary tumor.

**Keywords:** Crooke cell tumor, Cushing's disease, Depressive disorder, Guillain-Barré syndrome, Polyneuropathy, Psychiatric disorder.

## Highlights

- Physicians must not limit to one diagnosis in complex systemic clinical manifestations if it does not explain the whole clinical picture.
- Cushing syndrome represents a diagnostic challenge, insidious onsets might delay prompt identification of it, but it does not exclude other diseases or disorders.
- In a rare case of concomitant Cushing Syndrome and Guillain-Barré Syndrome, appropriate treatment of each lead to positive clinical development and outcomes.

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# Síndrome de Guillain-Barré como manifestación de enfermedad de Cushing secundaria a tumor de células de Crooke


## Resumen

**Introducción:** el síndrome de Guillain-Barré (SGB) es una enfermedad inflamatoria que afecta el sistema nervioso periférico y la enfermedad de Cushing (EC) es el tipo más común de síndrome de Cushing endógeno. Hay pocos informes en la literatura disponibles sobre la coexistencia entre ambos. Presentamos el caso de una paciente que desarrolló una polineuropatía compatible con síndrome de Guillain-Barré como manifestación de la enfermedad de Cushing secundaria a un tumor de células de Crooke.

**Objetivo:** reconocer que la mayoría de los casos de hipercortisolismo no tienen la presentación clínica típica. El personal de salud tiene que tener una alta sospecha para llegar a un diagnóstico temprano.

**Presentación del caso:** paciente de 64 años con diabetes mellitus tipo 2, hipertensión, trastorno depresivo mayor e intento de suicidio en el último año, que acudió al departamento de emergencias por una exacerbación de su trastorno del estado de ánimo después de una caída con lesión cerebral traumática sin pérdida de conciencia, debilidad progresiva simétrica, progresiva distal a proximal por síndrome de Guillain-Barré. Sin embargo, se documentó hipocalemia secundaria a enfermedad de Cushing causada por adenoma hipofisario. Se realizaron tratamientos con inmunoglobulina intravenosa y cirugía transesfenoidal. El estudio histopatológico confirmó un adenoma de células de Crooke productoras de ACTH. La movilidad, los electrólitos y el trastorno del estado de ánimo mejoraron después del tratamiento.

**Discusión:** este caso muestra una paciente con síntomas inespecíficos, presentación inusual de una patología conocida y con un origen etiopatológico infrecuente, por lo que vale la pena ser conocida y discutida

**Conclusiones:** el síndrome de Guillain-Barré suele ser esporádico. Hay pocos casos que documenten la coexistencia entre la enfermedad de Cushing y el síndrome de Guillain-Barré, siendo este el primer caso que describe un tumor pituitario productor de ACTH del tipo células de Crooke.


**Palabras clave:** tumor de células de Crooke, enfermedad de Cushing, trastorno depresivo, síndrome de Guillain-Barré, polineuropatía, trastorno psiquiátrico.

## Destacados

- Los médicos no deben limitarse a un diagnóstico cuando hay manifestaciones clínicas complejas y este no explica todo el cuadro clínico.
- El síndrome de Cushing representa un desafío diagnóstico, si tiene una instauración insidiosa puede retrasarse la identificación del mismo, pero esto no excluye que se presente con otras enfermedades o desórdenes.
- En un caso raro de síndrome de Cushing y Guillain Barré, el manejo apropiado de cada una de las entidades lleva a un curso y desenlaces clínicos positivos.

## Background

Guillain–Barré syndrome (GBS) is an inflammatory condition that impacts the peripheral nervous system. It is the leading cause of acute flaccid paralysis, with an annual incidence of 1 to 2 cases per 100,000 people. Diagnosis typically involves clinical signs, electrophysiological changes, and cerebrospinal fluid (CSF) abnormalities, such as albumin-cytological dissociation (1).

Cushing's syndrome (CS) is a rare condition characterized by a chronic course and systemic effects due to either endogenous or exogenous hypercortisolism. The most prevalent form of endogenous CS is Cushing's disease (CD), which is caused by an ACTH-secreting pituitary tumor (2-3). Crooke's cell adenoma (CCA) is a rare subtype of pituitary adenomas, accounting for less than 1% of all cases (4). These tumors may either secrete adrenocorticotropic hormone (leading to Cushing's disease) or be endocrinologically inactive. They are often invasive, can be clinically aggressive, and tend to recur, with a low success rate for cure after reoperation or radiotherapy (5).

Few reports in the literature address the coexistence of CS and GBS. Below, we present a case of a patient with psychiatric disorders

who developed GBS-like polyneuropathy as a manifestation of Cushing's disease secondary to a Crooke's cell tumor.

## Case presentation

### Initial assessment

A 64-year-old female patient with type 2 diabetes mellitus, hypertension, and major depressive disorder, who attempted suicide in the past year, presented to the emergency department a month prior. She reported symptoms of sadness, irritability, aggressiveness, loss of appetite, fatigue, and progressive, symmetrical, distal-to-proximal weakness in her lower limbs, eventually affecting her upper limbs. This weakness resulted in a fall from a height, causing a traumatic brain injury (TBI) secondary to the muscle weakness, although she did not experience a loss of consciousness.

Following the trauma, she developed disorientation and experienced significant limitations in performing daily activities, requiring assistance. On physical examination, the patient was disoriented to time, place, and person. Cranial nerve function was intact. She displayed symmetrical, progressive motor impairment starting distally and moving proximally, with a positive Babinski sign (extensor plantar response). Muscle strength was reduced, graded as 3/5 in the upper limbs and 2/5 in the lower limbs. Reflexes were generally hypoactive, and there were deficits in vibration and proprioception.

### Diagnosis

On admission, a non-contrast cranial CT scan revealed a chronic right frontoparietal subdural hematoma without significant mass effect. Cerebrospinal fluid analysis demonstrated elevated protein levels (180 mg/dL), a cell count of 1 cell/mm$^3$, and glucose of 83.10 mg/dL. Refractory hypokalemia was identified and managed, but severe weakness persisted. Electromyography and nerve conduction studies showed findings consistent with left peroneal nerve mononeuropathy, supporting the diagnosis of Guillain-Barré Syndrome. Additionally, Urinary free cortisol levels were markedly elevated at 2027.4 µg/24 hours (Reference Value: 4.3–176 µg/24 hours), with post-1 mg dexamethasone cortisol levels of 31.3 µg/dL and ACTH levels of 37.56 pg/mL, confirming ACTH-dependent Cushing's syndrome (Table 1 – Relevant laboratory test results). Hypokalemia was attributed to hypercortisolism. Hypophyseal MRI revealed an 8 mm microadenoma on the right side of the gland (Figure 1 – T1-weighted magnetic resonance). In the context of an atypical and severe presentation, with biochemically confirmed hypercortisolism and a medium-sized pituitary lesion, petrosal sinus catheterization was considered, which further confirmed central hypercortisolism, solidifying the diagnosis of Cushing's disease (Table 2 – Petrosal sinus catheterization results).

### Treatment

The patient underwent a five-day course of intravenous immunoglobulin therapy, resulting in significant improvement in her previously described weakness. Refractory hypokalemia persisted and was managed with both intravenous and oral potassium supplementation, maintaining potassium levels at the lower end of the normal range. Following the confirmation of Cushing's disease, transsphenoidal surgery was performed approximately 60 days after admission without immediate complications. Histopathological analysis revealed an adenoma characterized by small foci of grouped cells, loss of the reticular pattern, PAS-positive material adjacent to the nucleus, nuclear atypia, and a perinuclear ring of pale hyaline material. Immunohistochemical staining demonstrated ACTH immunoreactivity, confirming the diagnosis of an ACTH-producing Crooke's cell adenoma. Shortly after surgery, hyperkalemia resolved completely.

**Table 1.** Patient's relevant laboratory test results

| Laboratory | Patient's result | Reference value |
|---|---|---|
| Hemoglobin (g/dL) | 14.1 | 11.2-15.7 |
| Creatinine (mg/dL) | 0.39 | 0.51-0.95 |
| Blood Urea Nitrogen (mg/dL) | 22.0 | 8-23 |
| Potassium (mmol/L) | 2.07 | 3.5-5.1 |
| Sodium (mmol/L) | 142 | 136-145 |
| TSH (uUl/mL) | 0.654 | 0.27-4.2 |
| Renin (pg/mL) | 16.14 | 2.64-27.66 |
| Aldosterone (ng/dL) | 2.39 | 2.52-39.2 |
| Glycosylated hemoglobin (%) | 10.64% | <5.6 |
| Prothrombin time (seg) | 10.9 | 9-12.5 |
| INR | 0.95 | |
| Partial thromboplastin time (seg) | 27.2 | 25.1-36.5 |
| ALT (U/L) | 54 | 0-31 |
| AST (U/L) | 26.2 | 0-32 |
| Free cortisol in urine 24 hours (ug/24H) | 2027 | 4.3-176 |
| Basal Cortisol (ug/dL) | 4.8-19.1 | 34.1 |
| ACTH (pg/mL) | >1500 | 4.7-48.8 |
| ACTH (pg/mL) | 37.56 | 4.7-48.8 |
| Basal Cortisol prior to dexamethasone (ug/mL) | 34.0 | 4.82-19.5 |
| Basal Cortisol post dexamethasone (ug/mL) | 31.4 | 4.82-19.5 |

**Note.** * TSH: Thyroid stimulating hormone; INR: International normalized ratio; AST: aspartate aminotrase; ALT: alanineamine transferase; ACTH: adrenocorticotropic hormone.

**Source:** own elaboration.

**Table 2.** Petrous sinus catheterization results

| | Right Petrous Sinus | | | Left Petrous Sinus | | | Peripheral | | |
|---|---|---|---|---|---|---|---|---|---|
| Time | ACTH (pg/ml) | Prolactin (ng/ml) | Ratio | ACTH (pg/ml) | Prolactin (ng/ml) | Ratio | ACTH (pg/ml) | Prolactin (ng/ml) | Ratio |
| **Basal** | 548 | 69 | 7,9 | 378 | 65 | 5,8 | 107 | 39 | 2,7 |
| **3'** | >1500 | 66 | 22,7 | 936 | 52 | 18 | 98 | 34 | 2,8 |
| **5'** | >1500 | 72 | 20,8 | 934 | 45 | 20 | 84 | 34 | 2,4 |
| **10'** | >1500 | 108 | 13,8 | 1158 | 56 | 20 | 125 | 31 | 4,0 |
| **15'** | >1500 | 39 | 38 | 847 | 85 | 9,9 | 380 | 30 | 12,6 |

**Note.** *ACTH: adrenocorticotropic hormone.
**Source:** own elaboration.

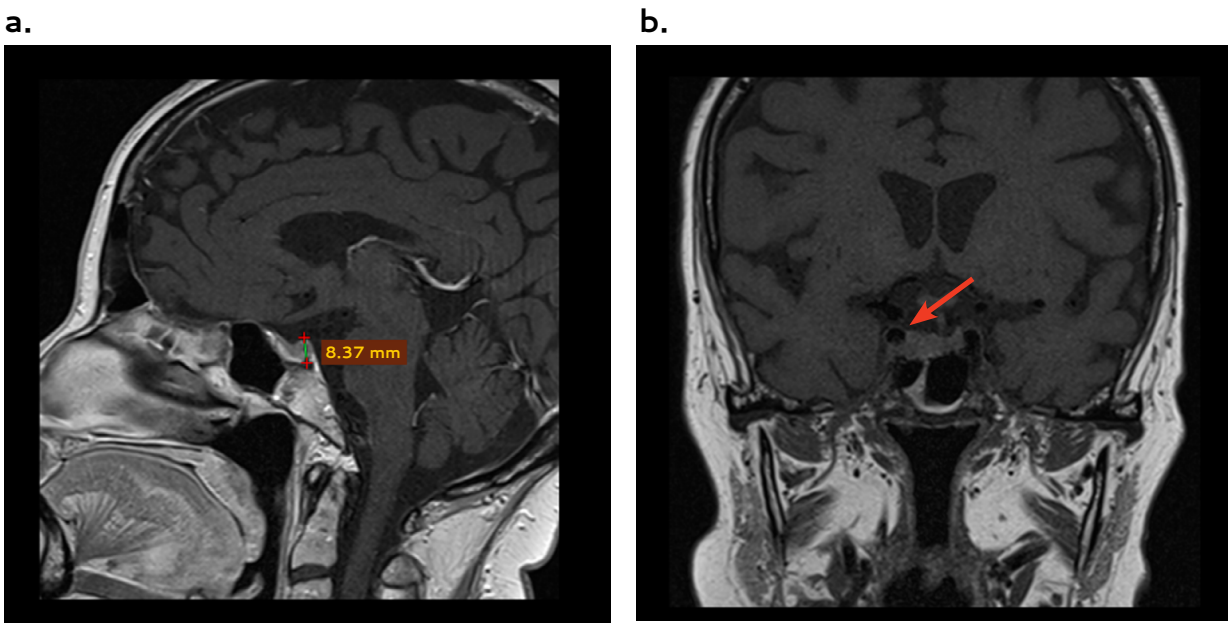


**Figure 1.** MRI of the sella turcica, T1 sequence

**Note.** Figure 1 a. T1-weighted magnetic resonance sagittal section of the sella turcica after the application of contrast medium in dynamic sequences. An 8-mm nodular lesion is observed in the right lateral portion of the sella turcica that has less enhancement than the pituitary parenchyma. Figure 1-b. T1-weighted magnetic resonance coronal section of the sella turcica. An isointense nodular lesion is observed in the pituitary parenchyma in the sequence without contrast. In addition, there was a deviation of the pituitary infundibulum (red arrow) to the left (contralateral to the lesion).
**Source:** The authors.

## Follow-up and outcomes

One month later, the patient underwent transsphenoidal surgery for resection of a microadenoma, which was completed without intraoperative complications. She had a positive postoperative recovery, with improvements in mobility, electrolyte balance, and mood disorder. At the time of discharge, neurological examination showed an improvement of strength, sensitivity, and proprioception.

## Discussion and conclusions

Dr. Harvey Cushing first identified Cushing's syndrome in 1932 based on clinical observations of a distinct phenotype in patients, which was subsequently linked to adenomatous growths in the pituitary gland (6). CS is an entity with a low prevalence and an incidence of 2-3 patients/ million population. CS is more common in women (3:1) during the third and fourth decade of their life (7). The high prevalence of diseases that have overlapping clinical characteristics with CS, such as obesity, metabolic syndrome, diabetes, and polycystic ovary syndrome, may compromise its early diagnosis (8). It is estimated that the prevalence of undiagnosed CS is 76 people/million population, or 24,000 people worldwide (9).

Neurological and psychiatric signs and symptoms were noted in the earliest publications on Cushing's syndrome, reflecting their presence within the spectrum of clinical manifestations (4). t has been demonstrated that several higher mental functions are impaired at the time of diagnosis (10). Affective disorders constitute the most frequent psychiatric complications of CS (4); depression can reach a prevalence of 57% - 68% of patients. In 12% of cases, depression is the first manifestation of CS (5). Our patient had a long-standing depressive disorder and a history of a suicide attempt in the year prior to the consultation. We do not rule out the possibility that her depressive symptoms were an early manifestation of Cushing's disease.

Guillain-Barre syndrome is a polyradiculopathy that affects the function of the sensory and motor systems, and the symptoms can vary from weakness of the limbs and cranial nerves to respiratory compromise and death. The study of the CSF shows cytological albumin dissociation (11-12). In our patient, a progressive ascending weakness was observed, with clinical examination revealing decreased strength in the lower limbs, greater than in the upper limbs, but symmetrical. Additionally, generalized hyporeflexia was documented, which could have contributed to the patient's fall. Since the weakness persisted even with serum potassium levels within the lower limits of normal ranges, we excluded this electrolyte disturbance as the underlying cause. Also, according to Asbury's criteria our patient presented progressive bilateral weakness of arms and legs, decreased tendon reflexes in affected limbs, progressive phase lasts of more than 4 weeks, increased protein level in cerebrospinal fluid with only one mononuclear cell, and electrodiagnostic features of motor neuropathy (13). Infectious and immunological triggers, malignancies, and pregnancy have been described as disease initiators (14). There are a few cases reports documenting concomitance between CS and GBS, two from the Lahey Clinic and another from the Mayo Clinic in 1959 (15). In these case reports, a respiratory infection was documented as a precipitating factor, and CS preceded neurological compromise; in our case, it was not possible to document infection as the cause of GBS. Subsequently, a report was published in Iran in 2020 that described the case of a pregnant patient (16) with a subacute viral infection that was documented as the initiator, although pregnancy could also have play an important role.

In the patients described with concomitant GBS and CS, adrenal hyperplasia was identified. In our case, ACTH-dependent CS was confirmed, with imaging studies revealing a sellar adenoma consistent with CD. Due to the atypical and severe clinical presentation, inferior petrosal sinus sampling was performed, which further corroborated the diagnosis. This is the only reported case of this type to date. A histopathological study revealed a Crooke cell-type ACTH-producing pituitary tumor. This type of tumor is very rare, accounting for less than 1% of pituitary adenomas (17-18). Currently, no classification system exists to predict its

behavior. However, there are characteristics such as young age, severity of the disease, presence of depression, a high urinary cortisol level, and posttreatment ACTH that could increase the risk of recurrence (19). In some cases, this type of tumor may be clinically silent; however, in others, like in this patient, they can function as ACTH-producing tumors. These tumors are typically aggressive, with a high recurrence rate and a low likelihood of cure despite surgical interventions and/or radiotherapy (20). Currently, our patient remains under follow-up without evidence of relapse.

## Comment

Cushing syndrome is a diagnostic challenge to clinicians given the wide range of clinical manifestations such as obesity and diabetes, and neuropsychiatric symptoms. Guillain-Barre syndrome is a polyradiculopathy that affects the function of the sensory and motor systems most of the cases are sporadic but there are a few cases reports documenting concomitance between CS and GBS.

## Author's contributions

Guillermo Guzmán: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft; Veline Martínez and Luis Escobar: Investigation, Methodology, Writing – Review & Editing; Raúl Assad and María Alejandra Urbano: Resources, Writing – Review & Editing; María Angélica Guerra: Project Administration, Validation, Writing – Review & Editing. All authors have read and approved the final manuscript, ensuring its accuracy and integrity.

## Ethical Statement

This study reported data of human tissue. It was approved by the Fundación Valle del Lili's ethics committee with the protocol number 539. Consent was necessary for the approval.

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

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## Conflicts of interest

The authors of the text explicitly declare that there is no conflict of interest that could compromise the impartiality and validity of the article in question. This statement encompasses any financial, personal, or institutional relationship that could exert undue influence on the research and publication process.

## Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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