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## CASE REPORT

# COVID-19 Complicating Cushing Syndrome in a Nigerian Infant: A Case Report

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## Summary

Cushing syndrome (CS) is an uncommon morbidity in children. As a result of this rarity, there may be a delay in making the diagnosis or it may be missed completely resulting in progression to life-threatening complications. COVID-19 is an infectious disease that is currently the cause of a global pandemic although it affects children less commonly than adults. Our patient developed CS in early infancy which was diagnosed by elevated serum cortisol and left adrenal adenoma on abdominal magnetic resonance imaging (MRI). Unfortunately, the diagnosis of CS was missed earlier thereby delaying treatment and she also contracted the COVID-19 infection. The presence of these two medical conditions in a very young child may have resulted in a more advanced diseased state and increased chances of a poor outcome. A high index of suspicion for CS is necessary to forestall delay in commencement of appropriate treatment. Parental consent was obtained to publish this report.

*Keywords: Adrenal adenoma, Children, Coronavirus, COVID-19, Cushing syndrome.*

## Introduction

Endogenous Cushing syndrome (CS) is a rare life-threatening disease in childhood. [1] It is caused by prolonged and excessive cortisol production from various sources as described by Harvey W. Cushing in 1932. [2,3] Globally, the incidence of CS is about 2-5 new cases per million per year and a tenth of the new cases occur in children. [4] Pituitary adenoma accounts for 75% of CS occurring in children above five years of age while a primary adrenal tumour is the

commonest cause of CS in children aged below five years. [1] CS has an insidious onset with weight gain and growth failure as the leading manifestations; other symptoms include changes in facial appearance (Cushingoid facies), striae, hirsutism and hypertension. [1] The detection of CS in children may be missed or delayed for a myriad of reasons; these may include a low index of suspicion as it is a rare disease, poor access to investigations and expert management either due to non-availability or high cost of care, especially in resource-constrained settings.

Coronavirus disease 2019 (COVID-19) is caused by a virus known as the Severe Acute Respiratory Syndrome Corona Virus (SARS-COV-2). It was first detected in Wuhan, China<sup>[5]</sup> and it is the cause of an ongoing pandemic. At the onset of the pandemic, it was unclear if children were spared from the effects of the virus as paediatric COVID-19 cases were uncommon. However, figures from the United States of America (USA) indicate that 7.3% of laboratory-confirmed cases occurred in children less than 18 years of age. <sup>[6]</sup> SARS-COV-2 infection associated with household contacts and healthcare workers has also been implicated as a source of disease transmission to children. <sup>[7]</sup> Even though it is thought that children suffer milder cases of SARS-COV-2 infection compared to adults, <sup>[8,9]</sup> it should be noted that fatal cases have also been reported among children. <sup>[10]</sup> The clinical features are similar in both adults and children with fever, cough and shortness of breath being reported as the commonest presentation in children.<sup>[9,10]</sup>

This report is about a case of Cushing's syndrome complicated with COVID-19 disease in an infant.

## **Case Description**

A one-year-old girl; the fourth child of her parents in a non-consanguineous Nigerian marriage, presented at the Premier Specialist Medical Centre, Lagos with a day history of fever and fast breathing. The fever was intermittent and relieved temporarily by antipyretics, there was no associated cough or seizure. The child was noted to have an inconsolable cry and had a reduced level of activity. In the preceding three months, she was noticed to smile less frequently, have increasing roundness of the face and excessive hair growth. She also regressed in previously attained developmental milestones of crawling and standing without support. There was no known history of the use of steroid-

containing cosmetics and medications in the child or any of the family members. The family used regular toilet soaps and bland creams, and they did not ingest herbal preparations. Pregnancy, delivery and immediate postnatal period were uneventful. However, she had recurrent clinic visits and hospital admissions from the fourth month of life on account of irritability and refusal to feed.

Physical examination showed a female infant with a rounded face, and fat pads on the arms and legs. She had excessive hair on her face, arms, legs and back. There were abdominal striae, areas of ecchymoses extending from the right hypochondriac region to the right inguinal region, healed bruises and perineal and axillary candidiasis (Figures 1 and 2). Her body temperature ranged from 36.6°C to 39.7°C. She cried excessively, had initial flat and normotensive anterior fontanelle which progressively became full during admission. Her body weight, body length and occipitofrontal circumference were 8.4kg (30<sup>th</sup> centile on the WHO Growth chart), 60.5cm (< 3<sup>rd</sup> centile), and 41cm (<3<sup>rd</sup> centile) respectively. She was in respiratory distress shown by tachypnea and increased work of breathing. Her respiratory and heart rates ranged from 50 to 84 cycles/minute, and 140 to 180 beats/minute respectively. Her blood pressure on admission was normal at 90/40mmHg, but she developed hypertension subsequently, with the systolic blood pressure ranging from 138 to 160mmHg and diastolic blood pressure from 83 to 120mmHg which were above the 99<sup>th</sup> centile for the age, gender and length. She was admitted and had laboratory tests including complete blood count, urine analysis and microscopy, chest radiograph, trans-fontanelle ultrasound scan and thyroid function tests, done.

A clinical diagnosis of Cushing's syndrome was made and she was referred to a tertiary facility (Lagos State University Teaching Hospital, Ikeja, Lagos) so she would have access to care by

paediatric endocrinologists and paediatric surgeons.

*Laboratory investigations*

The morning serum (08.00hours) cortisol level was 1164.20nmol (240 - 618nmol) and serum testosterone level was 0.73nmol/L (0.035-0.69nmol/L) respectively, while serum cortisol measured 1184.02nmol after an overnight dexamethasone suppression test. Thyroid function tests showed free serum T3, free serum T4 and serum Thyroid Stimulating Hormone (TSH) values of 4.72 pmol/L (4.4-7.3 pmol/L), 8.2 (7.2-16.4 pmol/L) and 1.3 (0.700-5.800 mIU/L) respectively. Full Blood Count showed leucocyte count of  $16.94 \times 10^9/L$  ( $4-11 \times 10^9/L$ ), Polymorphonuclear cells - 70.7%, Lymphocytes - 14.3%, Monocytes - 15%. Packed cell volume/Hemoglobin - 44.4%/14g/dl, and platelets count -  $214 \times 10^9/L$  ( $150-300 \times 10^9/L$ ). Initial serum electrolytes showed hypokalemia of

2.8mmol/L (3.5-5.0mmol/L). Subsequent serial serum electrolytes showed reducing serum sodium (126-108mmol/L) and serum chloride levels (85-68mmol/L) and normal serum potassium levels (3.5mmol/L). Urinalysis was normal and urine culture yielded no significant growth. Urine specific gravity ranged from 1.000 to 1.010. Lumbar puncture which was attempted much later in the course of admission was aborted due to cardiorespiratory compromise. Abdominal MRI (Figure 3) illustrates the soft tissue enhancing in the left adrenal mass demonstrating a significant signal drop on the opposed-phase chemical shift images, which is highly suggestive of lipid-rich adrenal adenoma, while no abnormality was detected on brain MRI. A diagnosis of CS from a left adrenal adenoma was made and suspected meningitis complicated by Syndrome of Inappropriate Antidiuretic Hormone (SIADH).



**Figure 1: Infant with a rounded face and generalised obesity**

*Treatment*

The child received the following medications; anti-hypertensive agents (Amlodipine, Propranolol, Spironolactone and Frusemide), and serial intravenous antibiotics (Ceftriaxone and Meropenem). Oral Ketoconazole was commenced for its cortisol lowering property.

Correction of hyponatraemia was instituted with sodium bicarbonate on account of the non-availability of hypertonic sodium preparations locally.

*Progress and demise*

Fever subsided about a week into admission but relapsed after two days with worsening dyspnea. Based on the suspicion of COVID-19 disease, nasopharyngeal samples were sent for testing. She remained critically ill and died after 21 days of admission. The result of the COVID-19 antigen

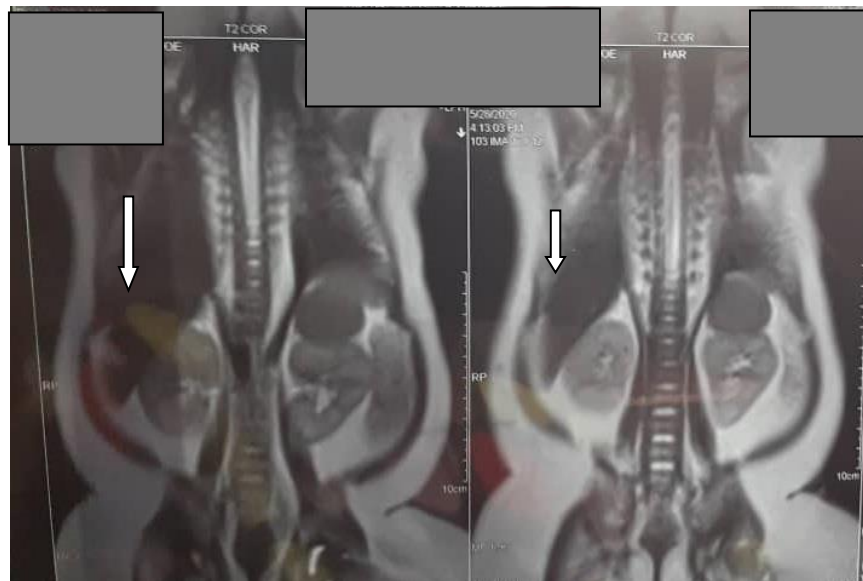
test retrieved post-mortem was positive; however, the parents of the infant tested negative to SARS COV-2 infection.

*Ethical consideration*

The consent to publish this case and the pictures of the baby was obtained from the parents.



**Figure 2: Arrows highlight the areas of ecchymoses**



**Figure 3: Soft tissue enhancing left adrenal mass as seen on abdominal MRI**

## Discussion

Cushing's syndrome is extremely rare in infants with less than 100 cases reported worldwide. [11] In children under five years of age, it is frequently caused by primary adrenal tumours, [12] while it is commonly caused by Cushing's disease (CD) from pituitary adenomas in children over five years old. [13] The clinical presentation of CS is due to excessive and prolonged cortisol production which in turn leads to the clinical findings of obesity, hirsutism, moon-shaped face, skin striae, growth failure and hypertension. [14]

Following established protocols, [1] the first step in confirming CS is to demonstrate elevated serum cortisol level. This is tested by assaying 24-hour urinary free cortisol, late-night salivary cortisol, and midnight plasma cortisol. [1] Also, low 8.00-9.00 am plasma cortisol level taken after an overnight 1mg dexamethasone suppression test excludes CS. [15] Cushing disease, on the other hand, is easily confirmed with elevated plasma ACTH. [1] Imaging studies [(Computed Tomography (CT)/ Magnetic resonance imaging (MRI)] are also required to identify the lesion. [16] In the index patient, the 8.00 am plasma cortisol level was elevated and the level remained high after 1mg overnight dexamethasone suppression test. The blood sample for plasma ACTH level was not drawn due to logistic reasons. However, the abdominal MRI demonstrated a unilateral adrenal tumour while the brain MRI was normal.

The main aim of treatment in CS in children is to normalize cortisol levels to allow for normal growth and to reduce the harmful effects of hypercortisolaemia. [16] This can be achieved medically and surgically. The index patient received oral Ketoconazole both as a cortisol lowering agent [4] and as an anti-fungal agent alongside conventional antihypertensive agents [16] with subsequent lowering of the blood pressure. She also received serial intravenous

antibiotics which were used empirically. [14] Antibiotics were used particularly in the index patient because of suspected but unproven meningitis. Hyponatraemia correction was started with sodium bicarbonate as hypertonic sodium preparations were unavailable locally. It was hoped that medical management would be successful and she would then have a definitive treatment of left adrenalectomy performed.

Hypercortisolaemia in CS predisposes to immunosuppression and the risk of infections [14,16] including meningitis and its complications; SIADH being one of them. SARS COV-2 infection is a disease that has been associated with immunodeficiency, obesity, hypertension and diabetes (effects of hypercortisolaemia) and may also be associated with CS as a co-morbidity. [14] The index patient had evidence of immunosuppression from the history of multiple hospital admissions and suspected meningitis. She also had hypertension, a cardiovascular feature of CS; this is the commonest cause of mortality in patients with CS. [16]

The index patient is one of the uncommon cases of infantile CS and the rarity of CS in infancy likely led to the earlier missed diagnosis of CS. She had co-morbidities of suspected meningitis and COVID-19 which increased her risk of mortality.

## Conclusion

Cushing's syndrome, although quite rare in children, should not be missed because it has peculiar clinical symptomatology. Therefore, there is a need for a high index of suspicion in children presenting with the classical symptoms to prevent delay in diagnosis and commencement of treatment. COVID-19 being a disease that often complicates chronic medical conditions has the potential to worsen the prognosis of CS especially in a young child.

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