# Conn Syndrome with Hyperthyroidism and Refractory Hypokalemia: A Case Report

Tamara Audrey Kadarusman[1]*, Satria Agung Maulana Fahmi[1], Rusdiyana Ekawati[2]

[1]General Practitioner, Petrokimia Gresik Hospital, Gresik, Indonesia
[2]Department of Internal Medicine, Petrokimia Gresik Hospital, Gresik, Indonesia

***Corresponding Author:***
*Tamara Audrey Kadarusman, MD. Petrokimia Gresik Hospital. Jl. A. Yani no. 69 Gresik 61119, Indonesia.*
*E-mail: audrey8397@gmail.com*

## ABSTRACT

*Conn syndrome is an adrenal gland adenoma that causes primary hyperaldosteronism, with a prevalence of <1% in the world population. Therefore, this case report presents a patient with Conn syndrome co-existing with hyperthyroidism. A 26-year-old female was admitted with muscle spasms in the left arm and muscle weakness in both legs for a day, palpitations, excessive sweating, nocturia, polyuria, and polydipsia. The patient had a history of hyperthyroidism for 10 years and routinely took anti-hypertension (Nifedipine), anti-thyroid, and potassium supplements. Physical examination showed the presence of hypertension. In addition, laboratory examinations revealed hypokalemia, slightly elevated FT4. The patient showed a high level of ARR (Aldosterone-Renin ratio; >30 ng/dL), consistent with primary hyperaldosteronism. Since abdominal USG revealed no abnormality, abdominal MRI with contrast was performed and showed an adenoma in the left adrenal gland. During admission, the patient had refractory hypokalemia despite various efforts to correct the defect. An anti-hypertension drug was then administered, particularly a mineralocorticoid antagonist receptor (Spironolactone). After the treatment, the patient had manageable hypertension and a normal potassium serum level, with no symptoms. Subsequently, discharge was then granted after 9 days of treatment, with a surgery schedule.*

*Conn syndrome with hyperthyroidism can cause refractory hypokalemia, which transforms into a challenge in patient management. With early detection and management, the outcome of this case is manageable.*

***Keywords**: Conn syndrome, Hyperaldosteronism, Hypokalemia.*

## INTRODUCTION

Conn syndrome is a primary hyperaldosteronism caused by an aldosterone-secreting adenoma in the adrenal glands. This condition was named after JW Conn, who first found a case of secondary malignant hypertension due to primary hyperaldosteronism in 1955. Several studies have shown that Conn syndrome is the most common cause of secondary hypertension, accounting for approximately 10% of the hypertensive population. However, there has never been a reported case of Conn syndrome with hyperthyroidism, which can worsen the output of serum potassium levels in a patient.[1-3]

## CASE ILLUSTRATION

A 26-year-old female was admitted to the hospital with muscle spasms in the left arm for a day. The patients had symptoms of weakness in both legs, palpitations, sweating, and frequent urination at night for 3-4 times. In addition, there was a history of hyperthyroidism, hypokalemia, and hypertension, with routine intake of anti-hypertension, anti-hyperthyroid, and potassium supplement treatments. None of the family members had these symptoms, and there was no history of food or medication allergies.

On physical examination, the blood pressure was 142/93 mm Hg, other vital signs were

normal, and the VAS score for arms was 3-4. Neurological examination result was normal, while hypokalemia 2.6 mmol/L (normal range: 3.5 – 5.3 mmol/L) was found. CBC count, random blood glucose level, liver and renal function test, atrium, and chloride levels were normal when admitted.

During admission, the thyroid levels were checked, which showed TSH level ranging from 2.84 µIU/mL (normal range: 0.35 – 0.51 µIU/mL), FT3 level was 2.88 pg/mL (normal range: 1.8 – 4.2 pg/mL), and FT4 level was 1.46 ng/dL (normal range: 0.5 – 1.4 ng/dL). The patient was also checked for Renin level, and the result was 1.96 (normal range: 0.25 - 5.82). The Aldosterone level was 60.27 ng/dL, and the Aldosterone-Renal-Ratio (ARR) was 30.75, proving that this case was a primary hyperaldosteronism.

For imaging examination, the patient had an abdominal USG, which showed normal results. In addition, an abdominal MRI with contrast was scheduled, and the result showed slight hyperintense in-phase and a drop in signal in the opposed-phase with a size of 1.73x1.58 cm. This did not show contrast enhancement in the left adrenal gland, indicating a unilateral left adrenal gland adenoma. Meanwhile, the right adrenal gland appeared normal.

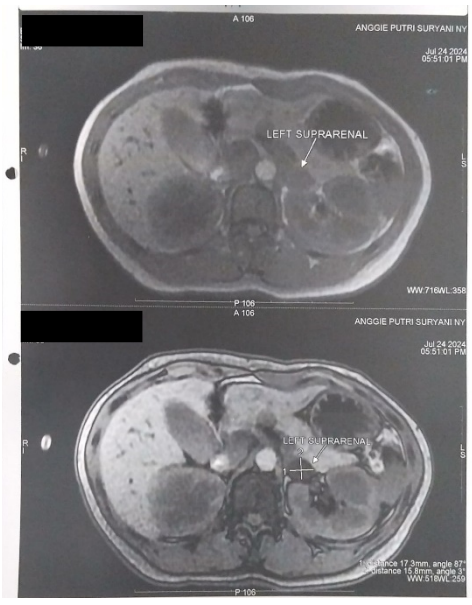


**Figure 1.** Abdominal MRI with contrast result of the patient, showing slight hyperintense in-phase, and drop signal to opposed-phase with size: 1.73x1.58 cm, not showing contrast enhancement, in the left adrenal gland, with the conclusion of cortical left adrenal adenoma.

On the first day of admission, the patient had a potassium infusion (KCl) with a dose of 25 mEq for 12 hours, repeated twice (first dose of potassium repletion). Following the first dose, potassium level became 2.7 mmol/L. The patient later had the second dose of potassium infusion, with the same dose as the previous one, repeated twice. Following the second dose, serum potassium level became 2.9 mmol/L. Despite repeated effort, potassium level only reached 2.5 mmol/L following the administration of the third dose.

Other than potassium infusion, the patient received potassium-sparing diuretics, also a mineralocorticoid antagonist, Spironolactone, with an initial dose of 25 mg per day. On the 7$^{th}$ day of treatment, the dosage was increased to 100 mg per day, and the patient received an anti-thyroid medication (Thiamizole) with a dose of 5 mg once daily, a dihydropyridine-type calcium-channel blocker anti-hypertension Nifedipine with a dosage of 10 mg once daily. In addition, an oral potassium chloride supplement with a dosage of 600 mg was given once daily. After the 9$^{th}$ day of admission, this case showed a promising outcome, and the patient improved well, showing manageable hypertension, normal potassium serum level, and no more symptoms presented earlier. The patient was then discharged from the hospital and planned to have a unilateral laparoscopic adrenalectomy.

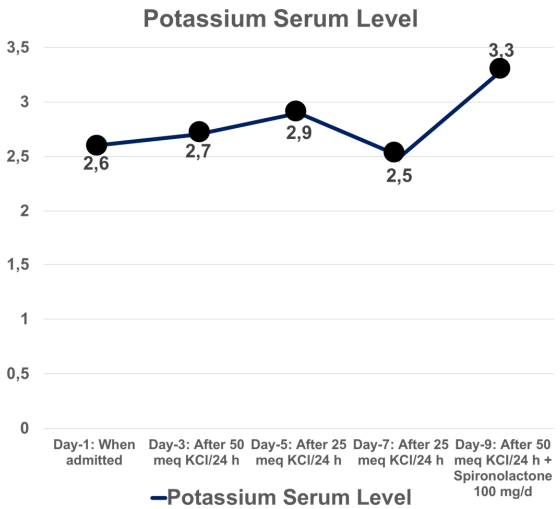


**Figure 2**. Potassium Serum Level of Patients Day-to-Day in Admissions

## DISCUSSION

Conn syndrome was defined as primary hyperaldosteronism syndrome caused by an aldosterone-producing adenoma of the adrenal glands. This was one out of many spectrums of primary hyperaldosteronism, and a condition in which there was a new source of aldosterone production. This syndrome was first found in 1954 by James W. Conn, who observed a patient with intermittent spasms and muscle spasms for 7 years, accompanied by hypertension and serial hypokalemia, as is observed in this patient today. Later discovered that it was caused by an aldosterone-producing adenoma in the adrenal glands, either unilateral or bilateral.[1,2,4-7]

The prevalence of Conn syndrome itself varied through many studies, ranging from <1% to 30% of cases.[2,4,8,9] However, there was an increase in the prevalence of Conn syndrome, since diagnostic tests were much more common in patients, even in primary care, and screening tests were held.[3,8]

There was no clear evidence of familial history of hyperaldosteronism in the patient's family, and the ultimate cause of the adrenal adenoma was still unknown.[10]

Conn syndrome arises when unilateral or bilateral adenoma(s) of the adrenal glands begin to overproduce aldosterone, a condition known as hyperaldosteronism. The body ignored RAAS due to the presence of a new, independent source of aldosterone. In addition, this binds to its receptors in the principal cells near the collecting duct of the kidney, causing an increase in Na+ and K+ channels on the luminal surface of the principal cells. This channel caused Na+ reabsorption, and by osmosis, H2O was also reabsorbed, causing slight hypernatremia and increasing arterial blood volume. Cardiac output was the product of heart rate and stroke volume, and when arterial blood volume was increased, this was increased, causing hypertension. Chronic arterial blood volume increase also resets the hypothalamic osmotic-sensitive ADH release, prompting lower ADH release, and leads the patients to polyuria and polydipsia. Na+/K+ channel placed in the collecting duct of the kidney also caused excessive K+ excretion through urine, causing severe hypokalemia, which also caused muscle cramps and even paralysis in patients.[1,4,11,14,15]

In the coincidence of Conn syndrome with hyperthyroidism, it was expected to have refractory hypokalemia. In addition, it was widely known that primary hyperthyroidism, showing high FT4 in such cases, could increase the activity of Na+/K+ pump in cells, causing a rapid intracellular shift of potassium, which could cause extracellular hypokalemia. Refractory hypokalemia in such patients needs continuous observation of their electrolyte balance.[11,16-18]

Clinical manifestations could vary from mild to severe muscle weakness, muscle cramps, paralysis, polyuria (several urinations at night), and polydipsia. Patients could present with hypertension, sometimes unresponsive to antihypertensive medications, with hypokalemia, and normal or slightly increased sodium level. Some could also show impaired glucose tolerance, showing high blood sugar levels.[1,12,19]

According to The 2016 Endocrine Society Clinical Practice Guideline in Primary Aldosteronism, it was recommended to do screening tests for primary hyperaldosteronism in patients with these criteria, 1) those with resistant hypertension (sustained blood pressure >150/100 mmHg) on every obtained on different days, 2) blood pressure > 149/90 mmHg despite 3 antihypertensives including a diuretic, 3) blood pressure <149/90 mmHg with 4 or more antihypertensives, 4) hypertension with adrenal incidentaloma, 5) hypertension and hypokalemia, 6) hypertension and sleep apnea, 7) family history of early-onset hypertension or stroke (<40 years), 8) hypertensive first-degree relatives of patients with primary aldosteronism. Components of screening included plasma aldosterone concentration (PAC) and plasma renin activity, then counting ARR (most recommendations in morning venous sample). The consensus in ARR was cut off, but most literature used > 30 (with Aldosterone as ng/dL and Renin as ng/mL/h), indicating primary aldosteronism. Elevated plasma aldosterone could be caused by the overproduction of this hormone by an adrenal adenoma, and suppresses the production of renin. In a meta-analysis by Hung et al. in

2021, it was said that ARR had an important role in diagnosing Conn syndrome, which had high specificity but varied in sensitivity.[6,20,21]

When a patient had a positive result for ARR, it was recommended to have one or more confirmatory tests to confirm the diagnosis. However, when spontaneous hypokalemia, undetectable renin plasma, and PAC > 20 ng/dL, there was no need for further confirmatory testing.[20]

After it is confirmed that the patient has primary aldosteronism, it is important to do radiologic imaging with a computed tomography (CT) scan, focusing on the adrenal glands. [1,6,7,20] Adrenal imaging could be done by a CT scan. This is considered safe, non-invasive, and very useful to diagnose primary hyperaldosteronism. In addition, it is said that CT scans focusing on adrenal glands with thin (< 3.00 mm) image slices showed 80-85% sensitivity and 70-75% specificity. A CT scan could find some subtypes of adrenal gland possibilities, such as normal adrenal glands, unilateral adrenal macroadenoma (diameter > 1 cm), bilateral adenomas, and minimal, unilateral adrenal limb thickening. The gold standard for diagnosing Conn syndrome is Adrenal Venous Sampling (AVS), usually performed before surgery. However, this was a very invasive procedure and could not able to be performed in all medical centers due to a lack of professional operators and hormonal markers.[22,23]

Treatment options to manage Conn Syndrome could be divided into 2, namely medications or surgery. These 2 options could vary from one health center to another, according to internal resources, facilities for surgery, and patient preference.[20]

Medical treatment options for Conn Syndrome could include mineralocorticoid receptor antagonists and spironolactone. Mechanisms of action of spironolactone were antagonizing the receptor and decreasing aldosterone synthesis. Usage of spironolactone with a dosage of 50 – 400 mg/day for 1-96 months showed improvements in patients with bilateral adrenal hyperplasia, with lower blood pressure. However, the dosage of spironolactone use could vary in several cases, due to a lack of consensus on spironolactone use for Conn syndrome. Moreover, there was reported gynecomastia with spironolactone therapy, because spironolactone was non-selective, and was anti-androgenic and agonist to progesterone.[4,24]

Surgical unilateral adrenalectomy, both laparoscopic and retroperitoneal, must be the primary option for Conn Syndrome patients

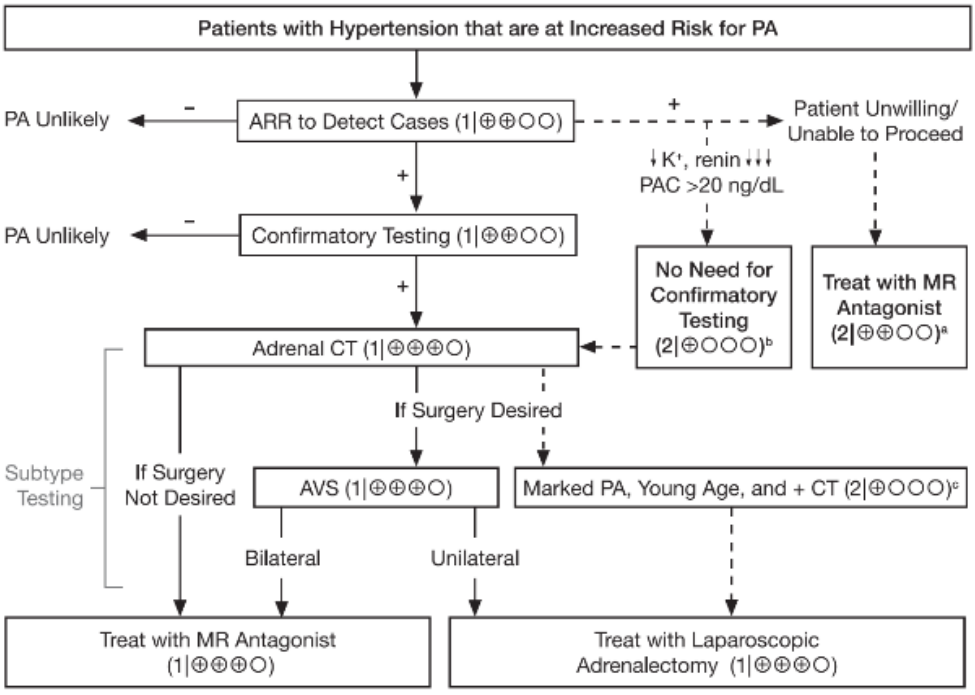


**Figure 3.** Screening pathways for patients with hypertension in whom Conn syndrome is suspected.[1]

with unilateral adrenal adenoma. This procedure was known to lower complication rates and shorten hospitalization days. Even today, robot-assisted laparoscopic surgery can be done for unilateral adrenalectomy. As an outcome of post-surgery management, patients showed normal potassium levels after surgery and more manageable hypertension, though some studies showed refractory hypertension even after surgery.[1,2,4,5,7,26-32]

The prognosis of Conn syndrome with hyperkalemia and hypertension depended very much on the choice of treatment. A study held by The Study Committee of Disorders of Adrenal Hormones in Japan involving 4,161 patients with primary hyperaldosteronism in Japan, showed that there was a benefit, in terms of reducing hypertension and hyperkalemia, in patients who underwent surgical treatment rather than medical treatment for unilateral adrenal adenoma.[24]

## CONCLUSION

In conclusion, Conn syndrome was represented as a unilateral adrenal adenoma, as one of many spectrums of primary hyperaldosteronism. Patients with these syndromes could develop a refractory hypokalemia with hypertension, despite all efforts to manage it. Early diagnosis and treatment were essential, and surgery must be considered since it showed promising outcomes for the patients.

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## CONFLICT OF INTERESTS

The authors declared that there was no conflict of interest.

## ETHICS STATEMENT

Informed consent was obtained from the patient and family to publish this case report.

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