Glucocorticoid Remediable Aldosteronism in a Family with a Strong History of Cerebral Aneurysms and Hypertension

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Received November 26, 2024; Accepted August 27, 2025.

Key words: Glucocorticoid remediable aldosteronism – Familial hyperaldosteronism type 1 – Primary aldosteronism – Hypertension – Cerebral aneurysm – Genetic testing – Mineralocorticoid receptor antagonist

Abstract: Glucocorticoid remediable aldosteronism (GRA) also known as familial hyperaldosteronism type 1 (FH1) is a rare genetic form of primary aldosteronism characterized by aldosterone overproduction regulated by adrenocorticotropic hormone (ACTH). We present the case of a 54-year-old woman with severe hypertension and hypokalemia. Genetic testing confirmed GRA by identifying a chimeric gene involving CYP11B1 and CYP11B2. This case highlights the importance of considering GRA in patients with resistant hypertension and a family history of cerebral aneurysms. Management involved glucocorticoid therapy and mineralocorticoid receptor antagonists, leading to significant improvement in blood pressure control.

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https://doi.org/10.14712/23362936.2025.23

Prague Medical Report / Vol. 126 (2025) No. 3, p. 151–154

Introduction

Glucocorticoid remediable aldosteronism (GRA) also known as familial hyperaldosteronism type 1 (FH1) is a rare, autosomal dominant form of primary aldosteronism (PA) caused by a chimeric gene resulting from unequal crossing-over between the CYP11B1 and CYP11B2 genes on chromosome 8q24.3. This genetic anomaly leads to aldosterone overproduction regulated by adrenocorticotropic hormone (ACTH), resulting in hypertension and hypokalemia typically presenting in early adulthood. GRA is associated with an increased risk of cerebral aneurysms and hemorrhagic strokes due to vascular remodeling effects of aldosterone (Dluhy and Lifton, 1999; Tan et al., 2023). Early diagnosis and management are crucial to prevent complications. We report a case of GRA in a patient with a significant family history of hypertension and cerebral aneurysms.

Case report

A 54-year-old woman was referred to our clinic for evaluation of severe hypertension and hypokalemia. She was diagnosed with hypertension at the age of 23 after experiencing episodes of light-headedness. Over the years, she had been treated with various antihypertensive medications, including atenolol 50 mg daily, hydralazine 100 mg three times daily, lisinopril 20 mg daily, hydrochlorothiazide 25 mg daily, a combination of amlodipine 10 mg and benazepril 40 mg daily, and chlorthalidone 25 mg daily, without achieving adequate blood pressure control. At the time of examination, the patient was taking atenolol 50 mg daily and amlodipine 10 mg daily and thanks to this major interactions of medications with laboratory testing were avoided. Spironolactone, eplerenone, or amiloride had not been previously tried.

Family history

The patient's family history was significant for hypertension and cerebral aneurysms (Figure 1). Her mother and father both died of ruptured cerebral aneurysms at ages 54 and 56, respectively. A maternal uncle and aunt also had cerebral aneurysms. Multiple family members were diagnosed with hypertension at a young age.

Laboratory investigations

On examination, her blood pressure was 180/100 mm Hg. Laboratory tests revealed:

- Serum potassium: 3.4 mmol/l (reference range: 3.5–5.0 mmol/l)
- Plasma renin activity: undetectable
- Serum aldosterone concentration: 17.6 ng/dl (reference range: 1–16 ng/dl)
- Aldosterone-to-renin ratio: 105 (reference range: <30)
- Adrenocorticotropic hormone (ACTH): 89 pg/ml

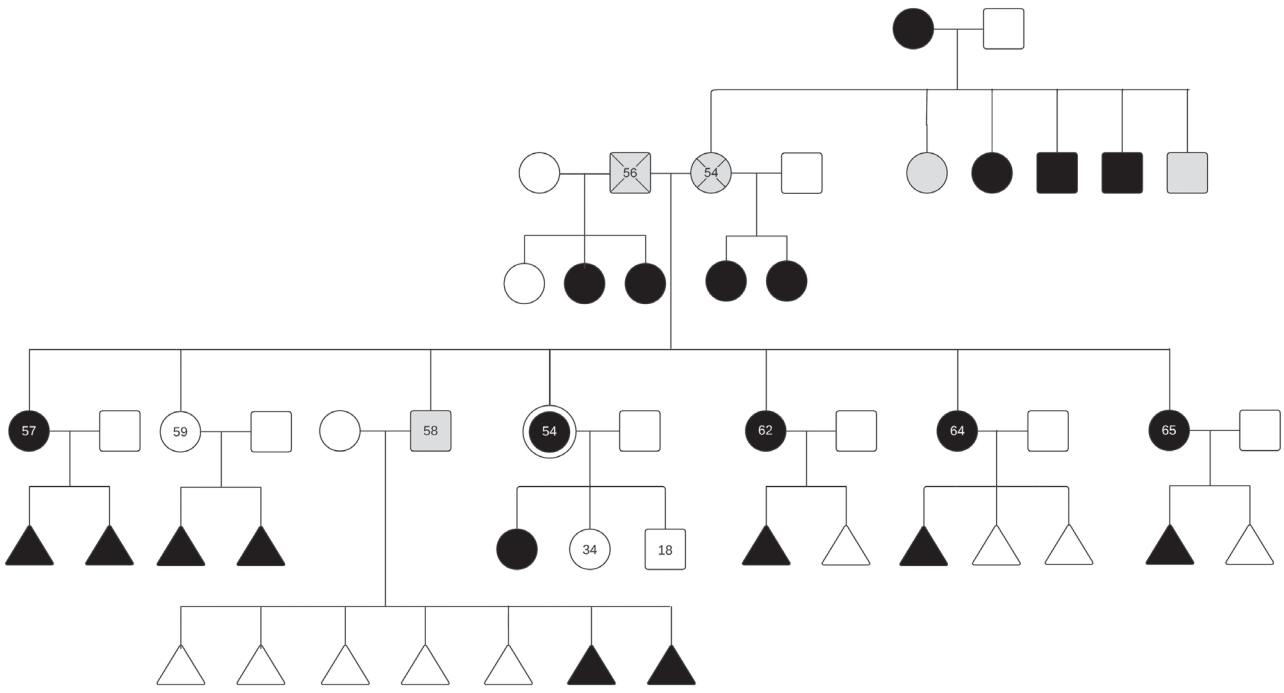

Figure 1: Genogram depicting the family history of hypertension and cerebral aneurysms.
White – no known hypertension or brain aneurysm; grey – known hypertension and brain aneurysm; black – known hypertension and no known brain aneurysm. Numbers signify the age in years of the patient and her family members at the time of evaluation.

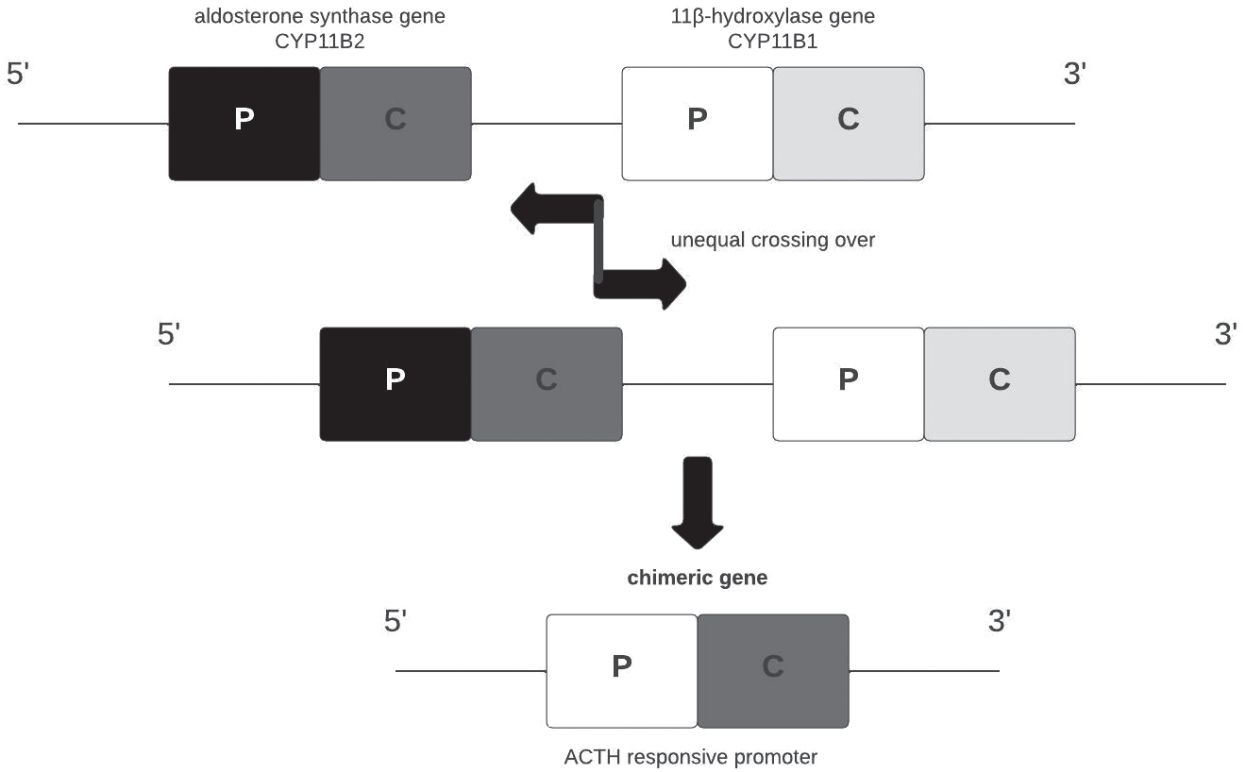

Figure 2: Chimeric gene.
P – promoter sequence; C – coding sequence.

A saline infusion test confirmed PA, with insuppressible aldosterone levels of 24 ng/dl, 21 ng/dl, and 18 ng/dl at 0, 1, and 4 hours post-infusion, respectively. An overnight 1 mg dexamethasone suppression test showed adequate cortisol suppression with a serum cortisol level of 1.0 µg/dl, ruling out cortisol-producing conditions. Serum metanephrines were normal.

Given the family history and laboratory findings, genetic testing was performed using polymerase chain reaction, revealing a chimeric CYP11B1/CYP11B2 gene (Figure 2), confirming the diagnosis of GRA.

Treatment

Initially, the patient was started on low-dose dexamethasone to suppress ACTH production, leading to improved blood pressure control. However, she experienced significant insomnia as a side effect. Spironolactone was then initiated but caused recurrent hyperkalemia. Eplerenone, a selective mineralocorticoid receptor antagonist, was introduced at 25 mg daily and gradually increased to 50 mg daily.

Outcome and follow-up

The patient's systemic blood pressure stabilized at around 130/80 mm Hg with eplerenone monotherapy. Serum potassium levels normalized to 4.0 mmol/l. Regular follow-up appointments were scheduled to monitor blood pressure, electrolyte levels, and potential medication side effects. ACTH levels were unfortunately not repeated following the initiation of the treatment.

Given the strong family history of cerebral aneurysms, magnetic resonance angiography (MRA) of the cerebral vessels was performed, which did not reveal any aneurysms. Genetic counselling was provided, and first-degree relatives were advised to undergo screening for GRA and cerebral aneurysms.

Discussion

This case underscores the importance of considering GRA in patients with resistant hypertension and a family history of early-onset hypertension or cerebrovascular events. The patient's presentation with severe hypertension and hypokalemia aligns with typical manifestations of GRA, a condition caused by a chimeric CYP11B1/CYP11B2 gene resulting in aldosterone overproduction under ACTH regulation (Lifton et al., 1992; Dluhy and Lifton, 1999; Tan et al., 2023). Interestingly in general patients with FH1 tend to be younger, more commonly female, have lower plasma aldosterone concentration, higher plasma renin activity, and less frequent hypokalemia compared to those with

sporadic primary aldosteronism (Araujo-Castro et al., 2024). The prevalence of FH1 ranges from 0.2 to 0.7% in various primary aldosteronism cohorts and may reach up to 4% in selected populations (Mulatero et al., 2011; Araujo-Castro et al., 2025). Genetic testing confirmed the diagnosis, consistent with findings by Lifton et al. (1992), who identified this genetic marker as definitive for GRA.

Treatment with low-dose glucocorticoids like dexamethasone effectively suppresses ACTH, reducing aldosterone production and managing hypertension (McMahon and Dluhy, 2004). However, our patient experienced significant side effects, necessitating the use of mineralocorticoid receptor antagonists. Eplerenone was preferred over spironolactone due to a better side effect profile, leading to marked improvement in blood pressure and normalization of potassium levels (Funder et al., 2016).

The association between GRA and an increased risk of cerebral aneurysms is well-documented (Litchfield et al., 1998; Mohan et al., 2015; Shahrrava et al., 2016). Excess aldosterone may contribute to vascular remodelling and arterial wall weakening, predisposing patients to aneurysm formation (Al Romhain et al., 2015). Given the patient's family history, screening for cerebral aneurysms using imaging modalities like MRA is essential. Early detection allows for timely intervention, potentially reducing morbidity and mortality.

Effective management of GRA requires a multidisciplinary approach involving endocrinologists, geneticists, and other specialists. Regular monitoring of blood pressure, electrolytes, and potential medication side effects is crucial for optimal patient care. Genetic counselling is recommended for family members, as early diagnosis can lead to preventive measures and improved outcomes.

Conclusion

GRA should be considered in patients with resistant hypertension and a strong family history of hypertension and cerebral aneurysms. Early diagnosis through genetic testing allows for targeted therapy, improving outcomes and preventing complications. Awareness of the increased risk of cerebral aneurysms in GRA patients highlights the importance of appropriate screening and preventive measures.

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