Adrenal Aldosterone-Producing Adenoma in a 14.5-year-old Boy With Familial Polyposis Coli (APC) Gene Mutation

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Abstract

A 14.5-year-old boy was evaluated with nonspecific gastrointestinal complaints and was incidentally found to have significant hypertension. He had a strong family history of adenomatous polyposis coli. Laboratory work-up revealed hypokalemia, alkalosis and suppressed plasma renin activity with slightly elevated serum aldosterone levels. An MRI of the adrenal glands showed a 9 x 5 x 8 mm hypointense oval mass in the left adrenal gland. Adrenal venous sampling demonstrated significant lateralization to the left adrenal gland. Laparoscopic left adrenalectomy was performed and pathologic examination of the specimen confirmed the diagnosis of APA. After surgery, the patient's blood pressure improved gradually. A molecular analysis demonstrated that he had adenomatous polyposis coli (APC) gene mutation (453 del A). APC gene mutation has been known to cause extra-colonic manifestations including nonfunctioning adrenal adenomas. Although one adult case has been reported previously, this is the first pediatric case reported in the literature with APC gene mutation and APA. APA is a very rare, curable cause of primary hyperaldosteronism in children. A careful family history and mutation analysis of APC gene should always be considered in all children with the diagnosis of APA because of the possible association with APC gene mutation.

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Introduction

Hypertension in the pediatric age group is most commonly due to renal disorders, and endocrine disorders as a cause of childhood hypertension constitute only <10% of the cases (1). Among the endocrine causes, primary hyperaldosteronism is very rare in the pediatric age group (1-3). Four causes of primary hyperaldosteronism have been recognized, including aldosterone-producing adenoma (APA), dexamethasone suppressible hyperaldosteronism (DSH), idiopathic hyperaldosteronism (IHA, also termed bilateral adrenal hyperplasia) and hyperaldosteronism caused by adrenal carcinoma (3). The most common cause of primary hyperaldosteronism in children is IHA(1-3). Although not uncommon in the adult population, APA in children is exceedingly rare, and only a few cases are reported in the literature (4-9). We describe a 14.5-year-old boy with a rare case of left adrenal aldosterone-producing adenoma. Interestingly, he had a family history of adenomatous polyposis coli and was found to carry a mutation of the adenomatous polyposis coli (APC) gene. Although familial adenomatous polyposis coli (FAP) has been known to cause extracolonic manifestations, including nonfunctional adrenal adenomas (10), APA is reported only in one adult patient (11). This is the first pediatric patient with an APC gene mutation presenting with APA.

Case Report

A 14.5-year-old boy was referred to pediatric gastroenterology for his complaints of constipation and occasional blood streaking after bowel movements. He had had no significant medical problems in the past and had been in good health. Family history was significant for familial adenomatous polyposis coli (FAP) of his father, paternal uncle, and paternal grandfather, and all had undergone total colectomies. His father also had a history of hypertension, hyperlipidemia and stroke. On physical examination, he was at the 50th percentile for height and 25th to 50th

percentile for weight. His blood pressure in the right arm was 168/106 mm Hg and in the left arm was 165/102 mm Hg. He was Stage 3 for pubic hair and genital development. The rest of his physical examination was unremarkable.

On laboratory tests, as summarized in Table I, he had hypokalemia, mild hypernatremia and alkalosis. Aldosterone levels, on the other hand, were at the upper end of normal on several occasions, and once above the normal range despite suppressed plasma renin activity. Plasma catecolamines and DMSA of the kidneys were normal. An MRI scan of the adrenal gland showed a 9 mm x 5 mm x 8 mm hypointense oval lesion in the left adrenal gland consistent with adrenal adenoma. Adrenal venous sampling was performed for definitive diagnosis of adrenal aldosterone-producing adenoma. As seen in Table II, the aldosterone to cortisol ratio (A:C) indicated significant lateralization of aldosterone production to the left adrenal gland. The ratio of A:C of the adrenal gland to the A:C of the inferior vena cava for the left side was 17.9, and for the right side was 0.44, which confirmed the diagnosis of left APA. A laparoscopic left adrenalectomy was performed with no complications.

There was a well-circumscribed adrenal adenoma measuring 1.2 cm x 1.0 cm x 0.9 cm in the left adrenal gland (Figure Ia and Ib). Postoperatively, his aldosterone level in peripheral blood was < 2 ng/dL with a renin level of < 0.6 ng/mL/h. The patient continued to have some residual hypertension for the next several days after surgery, which resolved gradually. A mutation analysis (Mayo Clinic Laboratories, Rochester, MN) demonstrated that he carries the adenomatous polyposis coli (APC) gene mutation (453 del A). About 2 months after surgery, at the time of colonoscopy, his blood pressure was 117/67 mm Hg. The colonoscopy revealed no mucosal changes or polyps and follow-up with repeat colonoscopies was planned because of the APC mutation.

Discussion

FAP is an autosomal dominantly inherited disorder with an estimated prevalence of 1:5000 to 1:17,000 (12). It is characterized by the presence of multiple, usually hundreds to thousands of adenomatous polyps in the large intestine (10,13,14). It is caused by mutations in the APC gene located on chromosome 5q21 (11,13,14). The APC gene is a tumor suppressor gene and both APC alleles must be inactivated by a mutation for the development of FAP (14). It is rare for FAP to present in childhood; polyps usually develop during the teenage years or early twenties (13,15,16). If the disease is left untreated, the average age for developing colon cancer is 39 years (13). Since the lifetime risk of developing colon cancer is close to 100%, surveillance colonoscopy is recommended in patients with a family history of FAP, and if disease is found, total colectomy is recommended (12).

The causal relationship between FAP and adrenal lesions is unknown. Patients with familial adenomatous polyposis are known to have extracolonic manifestations. Endocrine neoplasms, including pituitary gland tumors, as well as tumors of the pancreatic islets and adrenal cortex, are now recognized as part of the extracolonic manifestation associated with FAP (10, 13, 16). It is often difficult to determine the true incidence of adrenal tumors in FAP patients because most of these tumors are clinically asymptomatic; however, the prevalence of adrenal masses in these patients is higher than in the general population.

It has been shown that adrenal tumors are present in 7.4% of patients with FAP but in only 2.9 % of patients without FAP (10). Marchesa et al (10) retrospectively reviewed the charts of 738 patients with FAP and found that many of these patients had extracolonic manifestations, including 15 patients with an adrenal mass. These patients had a diagnosis of FAP at an average age of 33 years, whereas the median age at time of adrenal mass diagnosis was 46 years. Most of these adrenal tumors were nonfunctional or cortisol-producing tumors. However, there is only one adult case, a 58-year-old man, reported in the literature with FAP and APA (11).

The physiologic consequences of excessive production of aldosterone are suppression of renin release and angiotensin production, and increased distal tubular sodium reabsorption with renal potassium wasting and alkalosis (1-3). Among the four distinct types of primary hyperaldosteronism, including APA, IHA, dexamethasone-suppressible hyperaldosteronism, and hyperaldosteronism due to adrenal carcinoma, the most common cause of primary hyperaldosteronism in children is IHA (2,3).

IHA responds to medical therapy rather than requiring surgical resection, whereas APA is curable with unilateral adrenelectomy on the side of the tumor (1-3). Therefore, it is important to determine the etiology of the hyperaldosteronism for appropriate treatment.

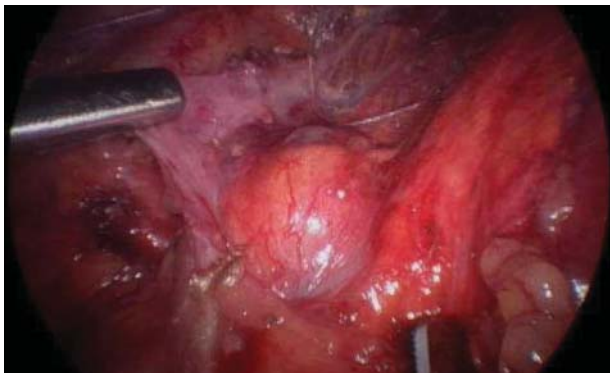

Figure Ia: Appearance of the adrenal adenoma on laparoscopy

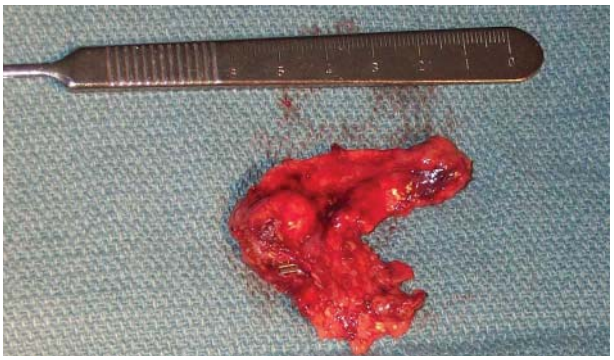

Figure Ib: Left adrenelactomy specimen with well-circumscribed adrenal adenoma measuring 1.2 cm x 1.0 cm x 0.9 cm

TABLE I: Laboratory test results

Laboratory Tests	**Normal Ranges**	**Results**
Sodium	(135-145 mEq/L)	140-149 mEq/L
Potassium	(3.0- 4.8 mEq/L)	2.5- 3.0 mEq/L
HCO3	(20-28 mEq/L)	31-33 mEq/L
Plasma renin activity	(1-5 ng/mL/h)	<0.6 ng/mL/h
Aldosterone supine	(1-22 ng/Dl)	15- 28 ng/dL
18 hydroxycorticoste-rone	(5-73 ng/dL)	103 ng/dL
Morning cortisol	(5-22 µg/dL)	13µg/dL
DHEA-S	(48-200 µg/dL)	57 µg/dL

TABLE II: Adrenal venous sampling results of patient with left adrenal aldosterone-producing adenoma

Site of sample	Aldosterone **(ng/dL)**	**Cortisol (µg/dL)**	**Aldosterone/ cortisol ratio (A:C)**
Left adrenal vein	1185	18.4	64.4
Right adrenal vein	59	36.7	1.6
Inferior vena cava	28	7.6	3.6

The differential diagnosis of hyperaldosteronism in children may at times be challenging. The clinical and laboratory findings of primary hyperaldosteronism due to IHA and APA are very similar. However, patients with APA tend to have more pronounced hypertension and hypokalemia than those with to IHA (1-3). The peripheral blood concentration of 18-hydroxycorticosteroid may behigh in APA but normal in IHA. Therefore, high concentration of 18-hydroxycorticosteroid supports but normal concentration does not rule out the diagnosis of APA (2,3). In the case presented here, the 18-hydroxycorticosteroid concentration in peripheral blood was high (Table 1), which supported the diagnosis of APA. Although one could argue about the necessity for adrenal venous sampling in presence of an adrenal mass demonstrated by adrenal imaging, it is still preferred by most pediatric endocrinologists for the definitive diagnosis in patients with primary hyperaldosteronism not only because APA is very rare in the pediatric age group but also because nonfunctional adenomas in adrenal glands are relatively common (2,17). In primary hyperaldosteronism, if the aldosterone concentration on one side is at least three times higher than the other side, it is highly suggestive of anadrenal adenoma rather than IHA (2,3,9). The aldosterone to cortisol ratio (A:C) is a more reliable param eter than aldosterone concentration alone to determine lateralization; it minimizes the technical errors caused by dilution of the adrenal venous sample by blood from the inferior vena cava on the right side or the inferior phrenic or renal vein on the left side (18). The A:C of adrenal glands to A:C of inferior vena cava should be at least 1.5 or more for the involved side and close to 1 for the other adrenal gland for the diagnosis of APA (19).

In the patient presented here, the ratio of the A:C of the left adrenal gland to A:C of inferior vena cava was clearly very high whereas very low on the right side.

The patient underwent laparoscopic removal of the tumor, which is a minimally invasive, effective and safe technique that allows faster recovery than laparatomic adrenalectomy (20). His blood pressure was elevated for several days postoperatively despite undetectable aldosterone concentrations in his peripheral blood. Studies have shown that residual hypertension can be detected in 11%-30% of patients with adrenal adenomas despite surgical resection, whereas hypokalemia resolves in nearly all cases (21, 22).

In conclusion, we present the first pediatric case of primary hyperaldosteronism due to APA as a result of an APC gene mutation. Although adrenal masses are known extracolonic manifestations of FAP, this is the first pediatric case of APA with APC mutation reported in the literature. Since APA is exceedingly rare in children, a careful family history and mutation analysis for APC gene deletion should always be considered in all children with the diagnosis of APA. Early recognition of FAP could prevent serious consequences related to colonic or extracolonic manifestations of the disorder.

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References

1. Rodd CJ, Sockalosky JJ. Endocrine Causes of hypertension in Children. Pediatr Clin of North Am 1993; 40 (1): 149-164.
2. Gill JR Jr: Hyperaldosteronism. In: Becker KL, ed. Principles and Practice of Endocrinology and Metabolism, Philadelphia, USA: Lippincott; 1990: 631-639.
3. Ganguly A, Grim CE, Weinberger MH. Primary aldosteronism. The etiologic spectrum of disorders and their clinical differentiation. Arch Intern Med 1982; 142: 813-815.
4. Kelch RP, Connors MH, Kaplan SL, Biglieri EG, Grumbach MM. A calcified aldosterone producing tumor in a hypertensive, normokalemic, prepubertal girl. J Pediatr 1973; 83: 432-437.
5. Bryer-Ash M, Wilson DM, Tune BM, Rosenfeld RG, Shochat SJ, Luetscher JA. Hypertension caused by an aldosterone-secreting adenoma. Occurrence in a 7-year-old child. Am J Dis Child 1984; 138: 673-676.
6. Decsi T, Soltesz G, Harangi F, Nemes J, Szabo M, Pinter A. Severe hypertension in a ten-year-old boy secondary to an aldosterone-producing tumor identified by adrenal sonography. Acta Pediatr Hung 1986; 27: 233-238.
7. Filiatrault D, Perreault G, Laberge JM, Ducharma JC. CT localization of an aldosteronoma in a 10 year-old boy. Pediatr Radiol 1986 16: 85-86.
8. Cemeroglu AP, Hopwood NJ, Cho KJ, at al. Aldosterone-secreting adenoma in a child diagnosed by an NP-59 Iodonorcholesterol Scan, adrenal venous sampling and spiral computed tomography. Endocrinologist 1996; 6: 405-409.
9. Li JT, Shu SG, Chi CS. Aldosterone-secreting adrenal cortical adenoma in an 11 year old child and collective review of the literature. Eur J Pediatr. 1994; 153:715-717.
10. Marchesa P, Fazio VW, Church JM, McGannon E. Adrenal Masses in Patients with Familial Adenomatous Polyposis. Dis Colon Rectum. 1997;40:1023-1028.
11. Alexander GL, Thompson GB, Schwartz DA. Primary Aldosteronism in a Patient with Familial Adenomatous Polyposis. Mayo Clinic Proc. 2000; 75:636-637.
12. Corredor J, Wambach J, Barnard J. Gastrointestinal polyps in children: Advances in molecular genetics, diagnosis, and management. J Pediatr 2001;138:621-628.
13. Kartheuser A, Walon C, West S, et alFamilial adenomatous polyposis associated with multiple adrenal adenomas in a patient with a rare 3' APC mutation. J Med Genet 1999;36:65-67.
14. Goss KH, Groden J. Biology of the Adenomatous Polyposis Coli Tumor Suppressor. J Clin Onc. 2000; 18:1967-1979.
15. Distante S, Nasioulas S, Somers GR, et al. Familial adenomatous polyposis in a 5 year old child: a clinical, pathological, and molecular genetic study. J Med Genet 1996;33:157-160.
16. Albuquerque C, Cravo M, Cruz C, et al. Genetic characteristics of patients with multiple colonic polyps. J Med Genet 2002; 39: 297-302.
17. Barzon L, Scaroni C, Sonino N, et al. Incidentally discovered Adrenal tumors.: Endocrine and Scintigraphic correlates. J Clin Endocrinol Metab 1998: 83: 55-62.
18. Filipponi, S, Guerrieri M, Arnaldi G, et al. Laprascopic adrenalectomy: a report on 50 operations. Eur J Endocrinol. 1998;138: 548-553.
19. Lo CY, Tam PC, Kung AW, Lam KS, Wong J. Primary Aldosteronism: Results of Surgical Treatment. Ann Surg. 1996;224:125-130.
20. Sawka AM, Young WF, Thompson GB, et al. Primary Aldosteronism: Factors Associated with Normalization of Blood Pressure after Surgery. Ann Intern Med. 2001;135:258-261.
21. Weinberger MH, Grim CE, Hollifield JW, et al. Primary aldosteronism, diagnoisis, localization and treatment. Ann intern Med 1979 90: 386-395.
22. Miller DL: endocrine angiography and venous sampling. Radiol Clin North Am 1993; 31: 1051-1067.