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CLINICAL STUDY

Juxtaglomerular cell tumor – a rare cause of secondary hypertension

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Abstract: Secondary hypertension (SH) is much more common in children than in adults. We report a 17-year-old girl with severe hypertension, hypokalemia and metabolic alkalosis. Because of these findings, primary or secondary hyperaldosteronism was suspected. Her initial treatment with spironolactone and ACE inhibitor was unsuccessful. With consideration of high plasma renin activity, the renal computed tomography angiography was performed and showed tumor mass in the left kidney. An uncomplicated partial left nephrectomy was performed. Histopathological examination and electron microscopy showed typical features of juxtaglomerular cell tumor (JCT). Imunohistochemistry of tumor was positive for CD34 and CD117 and this finding is effective in the diagnosis of JCT if immunostain for renin is unavailable. After the resection of JCT, the patient's blood pressure and hypokalemia returned to normal range. JCT is a rare renal neoplasm and an unusual cause of SH in children or adolescents *(Fig. 2, Ref. 12)*. Full Text in free PDF *www.bmj.sk.*
Key words: juxtaglomerular cell tumor, hypertension, hypokalemia, renin, immunohistochemistry.

Blood pressure (BP) measurements in children depend on age, height, gender, patient position, emotional stress, cuff bladder size, and type of sphygmomanometer. All pediatric textbooks recommend recording BP in all children older than 3 years during both health maintenance visits and emergency visits. Standards for systolic and diastolic BP are available in the Second Task Force Report (1). The prevalence of HT in children in general is estimated to be 1 – 3 %. Because morbidity and mortality is not usually seen in the pediatric hypertensive patient, it is important to identify surrogate markers for end-organ damage.

New evidence suggests that the most prevalent form of HT in pediatrics is essential/primary HT. The prevalence is increasing in concert with epidemic of childhood overweight and obesity (2, 3). However, there is always concern that some cases of secondary HT might be overlooked. Children and adolescents with secondary HT can have BP elevations ranging from mild to severe. Unless the pressure is sustained or is rising rapidly, HT is usually asymptomatic. With substantial HT, however, headache, fatigue, vomiting, epistaxis, dizziness, visual changes, and seizures may occur. Approximately 60–80 % of secondary HT in childhood is caused by renal parenchymal or renovascular disease. Juxtaglomerular cell tumor (JCT) or extrarenal renin-secreting tumors are unusual causes of secondary HT.

Case report

Family history of 17-year-old white female patient was unremarkable for HT, premature death, stroke or chronic renal disease. Birth history included the delivery of a normal term newborn with no pregnancy or delivery complications and no history of umbilical vein/artery catheterization. She was previously healthy and took no medications, including recreational drug use and oral contraception. Six months prior, she had developed head-

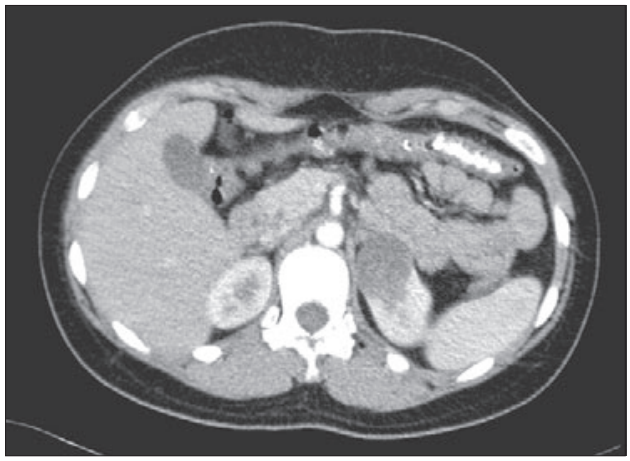

Fig. 1. Contrast-enhanced renal computer tomography showed low-density, well-circumscribed, solid lesion (diameter 33 mm) in the upper portion of the left kidney.

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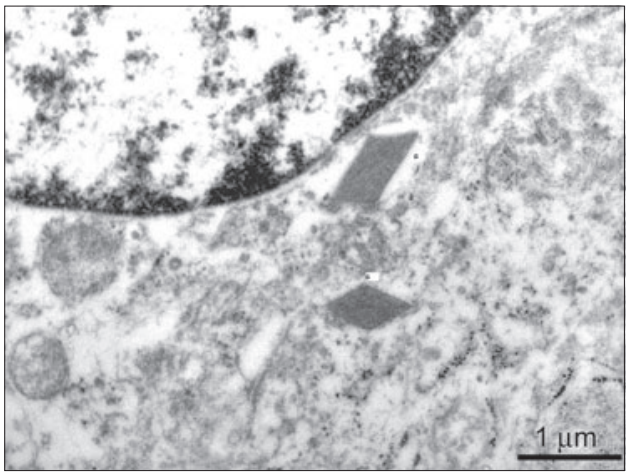

Fig. 2. Electron microscopy demonstrates characteristic rhomboid granules (G) from tumor tissue, magnification 40,000.

aches with intermittent vertigo. One week before the admission she had two short time episodes of collapse in a bathroom. She was not examined. Aunt of girl works as a nurse and she accidentally noted at home her high BP (226/178 mmHg, measurement by digital BP machine). The girl was referred to our department. On admission, her physical examination was 158 cm in height (–1.43 SDS [National Center for Health Statistics standard], 70.3 kg in weight (body weight/body height ratio +2.34 SDS) and body mass index 28.2 kg/m^2 (+2.79 SDS). She was normohydrated, fever free and had normal secondary sexual characteristics. Her skin examination showed no rash, ash leaf spot, or café-au-lait spots. Her heart rate was 130/min, respiratory rate 16/min, manual BP 220/180 mmHg (right arm) and the lower extremity BP 225/188 mmHg. Her lungs were clear, her cardiac rhythm without murmurs and her abdomen was soft without organomegaly. No edema was noted on the extremities. Neurological examination was normal. Fundoscopy of the eyes did not show any evidence of hypertensive retinopathy. Cardiac ultrasound showed mild left ventricular hypertrophy (mass: 89 g/m^2, normal: 61±17 g/m^2).

Initial serum biochemical studies (prior to start of antihypertensive therapy) were as follows: hypokalemia (K^+ 3.0 mmol/l), Na^+ 139 mmol/l, Cl^- 98 mmol/l, total calcium 2.32 mmol/l, phosphorus 1.29 mmol/l, magnesium 0.88 mmol/l, glucose 4.3 mmol/l, urea nitrogen 3.4 mmol/l, creatinine 58 ěmol/l, uric acid 205 ěmol/l and osmolality 277 mOsm/kg H_2O. Arterial blood gas revealed a mild metabolic alkalosis (pH 7.48, pCO_2 44 mmHg, pO_2 84 mmHg, HCO_3 26.3 mmol/l). Urinalysis revealed pH 6.5 and was negative for protein, glucose, blood or leukocytes. Patient's diuresis was 1840 ml/24 hrs and urine biochemistries showed low urinary output of sodium (22 mmol) and chloride (15.6 mmol) but high output of potassium (38.9 mmol). The transtubular potassium gradient (TTKG) was 7.4 (normal: 4.1–10.5). Red, white blood cell count, and platelets were normal. A renal ultrasound was normal, including duplex Doppler examination of renal blood flow. No abnormalities were found by ultrasonography of adrenal glands, pancreas, liver and both ovarium. A chest X-ray was normal. With consideration of HT, hypokalemia and metabolic alkalosis, we believed that the girl most likely had primary or secondary hyperaldosteronism. We performed next diagnostic procedure and sent girl's blood for detailed laboratory assessment. The therapy of arterial HT started with spironolactone and ACE inhibitor but HT was poorly controlled and calcium channel blocker was added. Still on combined antihypertensive therapy, the patient's BP was = 95 percentile for her age/height/gender. Six days after admission, additional laboratory parameters were reported. The patient's plasma renin activity (PRA) level in the upright position was increased (12.8 ng/ml/h, normal: 0.5–1.9 ng/ml/h) and the serum aldosterone was very slightly increased (0.63 nmol/l, normal: 0–0.60 nmol/l). The 24hrs urine for catecholamines, metanephrines, vanilmandelic acid and homovanilic acid was normal. Tumor markers (carcinoembryonic antigen, α-foetoprotein, β-human chorionic gonadotropin) were negative.

Because of the rising level of PRA, a contrast-enhanced renal computer tomography (CT) was performed showing a 33 mm low-density (25–30 HU), well-circumscribed, solid lesion in the upper portion of the left kidney, suggestive of a JCT/reninoma. With a preoperative diagnosis of reninoma, the girl underwent an uncomplicated partial left nephrectomy. Subsequently, histopathologic examination and electron microscopy (EM) confirmed the diagnosis of JCT (Figs 1 and 2). The diagnosis was also associated with a positive immunohistochemistry for CD34 and CD117. Immunostaining for renin was not available at our department.

During 3 days after operation, the patient's heart rate, BP and hypokalaemia had returned within normal range and antihypertensive medications were withdrawn. The girl is doing well 18 months after resection of JCT, her BP is still normal, PRA and serum aldosterone are in normal range. Her cardiac ultrasound shows a regression of left ventricular hypertrophy (mass: 71 g/m^2). We recommended a reduction of her overweight.

Discussion

Hypokalemia, defined as a plasma K^+ concentration below 3.5 mmol/, usually indicates a deficit in total body potassium but may also represent a shift of K^+ from the extracellular fluid to the intracellular fluid in the setting of normal body K^+ stores. Total body K^+ depletion causing hypokalemia result from an inadequate intake or from an excessive loss of potassium from the body via gastrointestinal tract or kidney. Ideally, assessment of urinary potassium excretion should be a timed, preferably 24 hrs collection. Especially in newborns and infants, the accurate collection of urine is difficult. In the absence of polyuria or hypovolemia, a random urinary potassium (U_K) of more than 20 mmol/l in the presence of hypokalemia generally indicates renal potassium wasting. Also, calculation of TTKG was recommended for the estimation of urinary potassium losses. TTKG of more than 4 in the presence of hypokalemia suggests an excessive renal losses of potassium. Urinary potassium wasting is often accom-

panied by a metabolic alkalosis (MAL). This is usually associated with an increased plasma aldosterone, which increases urinary potassium and acid losses, contributing to the hypokalemia and the MAL. The presence of primary hyperaldosteronism should be suspected in any patient with the combination of HT, metabolic alkalosis and hypokalemia. However, the degree of hypokalemia may be relatively subtle and a number of these patients may have normal plasma potassium. Further evaluation of these patients should include the estimation of PRA. The combination of hypokalemia, high PRA, HT and MAL is characteristic of renal artery stenosis and renin-secreting tumors. For next distinction between these two situations is possible to use plasma sodium because some patients with stenosis of renal artery have mild or severe hyponatremia (so-called: hyponatremia hypertensive syndrome). Usually, the Doppler examination is a "gold standard" for the diagnosis of stenosis of renal artery. Our patient had normal renal vascularization by duplex Doppler and tumor renal mass was showed by CT.

An excessive production of renin has been observed in several types of renal tumors (e.g., JCT, Wilms' tumor, mesoblastic nephroma, rhabdoid tumor of the kidney) and extrarenal tumors (e.g., liver hamartoma, ovarian adenocarcinoma, Sertoli cell tumor, lung and pancreatic cancer) (4, 5). Extrarenal renin-secreting tumors are exceptional in children. A MEDLINE search using keywords "extrarenal renin-secreting tumor" revealed in November 2009 only 7 reported cases with patients age range 10 –17 years. JCT is a rare benign tumor, especially in children and adolescents. Often was described a slight female predominance of 2:1 among affected patients (6). Patients with JCT may present with symptoms of HT or may be diagnosed with HT incidentally. Usually, the HT is severe and depending on the duration of HT, evidence of end-stage organ damage may be present. Hypokalemia and MAL are frequent laboratory abnormalities in patients with renin-secreting tumors. Often acombined various imaging modalities for localization of JCT is necessary, including ultrasound, renal arteriography, CT, and magnetic resonance imaging. The invasive studies with renal vein renin sampling has been used in some cases for localization of JCT. Because reninoma is usually small, so most of the tumor blood is collected into the peripheral veins and not in the renal vein. So renal venous sampling for renin is not mandatory due to high false negative results. Histopathological diagnosis of JCT is usually confirmed by a positive immunostain of renin or EM identification of renin granules (7, 8). However, some recent references report that JCT has a positive immunoreactivity with CD34 and CD117 antibodies (9). This positivity was demonstrated also in our patient. Our finding demonstrate that if immunostain of renin is not available, imunohistochemistry for CD34 and CD117 are effective at diagnosing JCT.

The appropriate treatment of JCT is tumor removal. Excellent results have been reported with wedge resection or tumor enucleation. Surgery is well tolerated, but cardiovascular instability, including BP changes during operation have been reported in some patients (10). Some investigators have advocated an avoidance of ACE inhibitors or calcium channel blockers on the day of surgery (11). Usually within 1 week after the resection of reninoma, there is normalization of HT and hypokalemia. The occurrence of JCT does not appear to confer any increased risk of HT in the future. To our knowledge, only one reported case describes an association between reninoma and myocardial infarction (12).

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