Case Report

A Case Report of Gordon's Syndrome in a 20-Year-Old Male with Free Medical Family History

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Gordon's syndrome is a rare autosomal dominant disease that manifests in childhood. It is characterized by hypertension, hyperkalemic hyperchloremic metabolic acidosis, low renin and usually normal aldosterone levels, and it is sensitive to thiazide diuretics. A 20-year-old male with a history of diagnosed Gordon's syndrome was referred to a nephrology clinic for evaluation. The patient, who was under treatment with hydrochlorothiazide, had been diagnosed with Gordon's syndrome at the age of 11, when he presented hypertension and episodes of hyperkalemic hyperchloremic metabolic acidosis. However, none of his relatives had been diagnosed with this syndrome. Therefore, we assume that our patient might be a case of *de novo* gene mutation.

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It is estimated that approximately 26% of the adult population worldwide suffer from arterial hypertension.[1] The great majority of these cases concern essential hypertension, whereas only 5-10% of adults with hypertension have a secondary cause.[2] In contrast, the prevalence of hypertension in childhood is only 1%[3] and the majority of the cases are secondary forms.[2,3] Renal parenchymal and renal vascular diseases are the most common causes in both children[2,3] and adults.[4]

A rare cause of secondary hypertension is Gordon's syndrome. Gordon's syndrome (or pseudohypoaldosteronism type 2, or familial hyperkalemic hypertension) is a rare autosomal dominant disease.[5-11] Its manifestations, which begin in childhood,[12] include hypertension (which may start 10 to 20 years later[8,10]), low renal potassium clearance and hyperkalemia, hyperchloremia, metabolic acidosis, low plasma renin levels, highly variable, but usually normal, plasma aldosterone levels,[6-9,12,13] and sometimes hypercalciuria.[5,6,8,10] Glomerular filtration rate and adrenal function are normal.[8,10-14] The disease is sensitive to treatment with low doses of thiazide diuretics and dietary salt restriction.[5,9,11,13,15] In this report, we present a case of a 20-year-old male who was diagnosed with Gordon's syndrome at the age of 11, but had no family history of this disease.

Case presentation

A 20-year-old male with diagnosed Gordon's syndrome joined the army as a newly-recruited soldier. None of his parents, his grandparents, his three siblings, or any other relative had been diagnosed with this syndrome. At the age of 11, he had episodes of dizziness and muscle weakness in combination with hyperkalemia (K^+ 6.4

mEq/L), but without any other findings from the clinical and basic laboratory examinations. After these episodes, he was referred to a specialized pediatric clinic. Clinical examination revealed developmental delay—body weight 27 kg (5th percentile), height 130 cm (3rd percentile), head perimeter 51.5 cm (50th percentile)—blood pressure 131/65 mmHg, heart rate 96 /min, and a mild end-systolic murmur. Accordingly, he underwent a more extensive investigation whose findings are listed in Table 1. The rest of the laboratory results, the radiographic and ultrasonographic findings for the kidneys, ureters and bladder, the intravenous pyelogram, electrocardiogram (ECG) and echocardiography were within the normal range. Moreover, the patient's systolic blood pressure was above the 95th percentile for his age in the 24h blood pressure examination, which is the threshold for hypertension in children.[3,16,17]

The patient was diagnosed as having pseudohypoaldosteronism type 2 (Gordon's syndrome), on the basis of his hypertension, hyperkalemia, hyperchloremia, metabolic acidosis, low urinary potassium excretion, normal plasma aldosterone levels, normal creatinine clearance (normal renal function), and relatively low rate of development. Thus, he was treated with thiazide diuretic (0.4 mg/kg/24h of hydrochlorothiazide daily). This led to normalization of all laboratory findings. The patient left the hospital after one month with corrected electrolyte values and acid-base balance (Na^+ 140 mEq/L, K^+ 4.4 mEq/L, Cl^- 103 mEq/L, pH 7.383, HCO_3^- 24.9 mEq/L, base excess 0.2) and was instructed to take 10 mg hydrochlorothiazide *per os* daily, and to observe dietary salt restriction and regular medical surveillance.

Nine years later, when he joined the army, he was referred to a nephrology clinic, where he stayed five days for evaluation. The clinical examination revealed no pathological features. His body weight was 70 kg and his height was 175 cm, indicating that his growth rate had increased after the initiation of treatment. For the assessment of his condition, the administration of hydrochlorothiazide was stopped on the first day and he underwent a laboratory investigation whose findings are listed in Table 2. Additionally, ultrasound examination of the kidneys, ureters, bladder and prostate was normal. The ECG and the remaining laboratory tests gave results within the normal range. Finally, his blood pressure levels were 130/70 mmHg, 130/80 mmHg, 115/75 mmHg, 145/60 mmHg, 145/75 mmHg for each day, respectively.

At the end of the fifth day, the treatment was restarted with *per os* administration of 12.5 mg of hy-

Table 1. Laboratory findings during the first hospitalization.

Type of sample	Parameter	Values	Normal values
Serum	Na^+	141	135-150 mEq/L
	K^+	6.3	3.5-5 mEq/L
	Cl^-	115	98-108 mEq/L
	Ca^{2+} (total)	10.1	8.4-11 mg/dl
	P	4.9	4-6 mg/dl
	urea	31	10-50 mg/dl
	creatinine	0.69	0.4-0.9 mg/dl
Plasma	renin (supine position)	32	5-47 μU/ml
	aldosterone (upright position)	11	3-28 ng/dl
Arterial blood	pH	7.29	7.35-7.45
	$PaCO_2$	34	35-45 mmHg
	HCO_3^-	17.7	22-26 mEq/L
	anion gap	10	10-14 mEq/L
	base excess	-7.7	-2-2 mEq/L
Urine	specific gravity	1026	1001-1030
	pH	4.81	4.6-8
	anion gap	54.5	-10-10 mEq/L
	FE_{Na}	0.5%	<1%
	FE_K	1.6%	6-19%
	proteins	7.3	0-20 mg/kg/24h
	creatinine	22	15-25 mg/kg/24h
	creatinine clearance	103.6	70-140 ml/min/1.73m^2

Na^+ – sodium; K^+ – potassium; Cl^- – chloride; Ca^{2+} – calcium; P – phosphorus; $PaCO_2$ – arterial partial pressure of carbon dioxide; HCO_3^- – bicarbonate; FE_{Na} – fractional sodium excretion; FE_K – fractional potassium excretion.

Table 2. Laboratory findings during the recent hospitalization.

Type of sample	Parameter	1st day	2nd day	3rd day	4th day	5th day	Normal values
Serum	Na^+	137	138	137	142.1	142	135-150 mEq/L
	K^+	4.6	4.8	4.5	4.54	5	3.5-5 mEq/L
	Ca^{2+} (total)	9.7			9.21	9.4	8.1-10.5 mg/dl
	P	2.7					2.5-4.8 mg/dl
	urea	29		34.6	36.2	43	10-50 mg/dl
	creatinine	1.4		1.1	0.99	0.9	0.7-1.5 mg/dl
Arterial blood	pH	7.411	7.448			7.39	7.35-7.45
	PaO_2	104	106.3			90.3	80-100 mmHg
	SO_2		99.2%			97.2%	95-100%
	$PaCO_2$	38.5	43.1			42.8	35-45 mmHg
	HCO_3^-	24	30.1			25.1	22-26 mEq/L
	anion gap	9.8				5.7	10-14 mEq/L
	base excess	0				0.4	-2-2 mEq/L
Urine	specific gravity	1024					1001-1030
	pH	5					4.6-8
24h-urine (previous day)	urine volume		700			1400	400-3000 ml/24h
	Na^+		34.8				40-220 mmol/24h
	K^+		36.9			52.9	25-125 mmol/24h
	FEK		1.26%			0.5%	6-19%
	Ca^{2+}		48				100-300 mg/24h
	creatinine		888			1904	800-1800 mg/24h
	proteins					52.8	0-150 mg/24h

Na^+ – sodium; K^+ – potassium; Ca^{2+} – calcium; P – phosphorus; PaO_2 – arterial partial pressure of oxygen; SO_2 – oxygen saturation; $PaCO_2$ – arterial partial pressure of carbon dioxide; HCO_3^- – bicarbonate; FE_K – fractional potassium excretion.

drochlorothiazide once, because his serum K^+ had reached the highest normal levels (5 mEq/L) and the FE_K (fractional excretion) values had been very low (0.5%). The patient left the hospital on the sixth day with instructions for continuation of the *per os* hydrochlorothiazide treatment as he used to take it (6.25 mg/12h) and regular medical surveillance.

Discussion

There are four subtypes of Gordon's syndrome, according to the mutated gene locus: a) 1q31-42, b) 17p11-q21, c) 12p13, d) unknown locus.[5,9,10] The second and third subtypes are due to mutations in the genes of with-no-lysine^K (WNK) kinases 4 (missense mutations) and 1 (deletions in the first intron), respectively,[5,9-11,13,18] which have a wide tissue distribution.[5,7,8,10,11,19] In the kidneys, they are located primarily in the distal nephron,[5,6,10,11,18] affecting the activity of many ion channels through regulation of their cell surface expression.[5-11,19,20] WNK4 decreases the activity of the Na^+-Cl^- cotransporter (NCC) (Na^+ and Cl^- reabsorption), the renal outer medullary potassium channel (ROMK) (K^+ excretion), and the epithelial sodium channel (ENaC) (Na^+ reabsorption), whereas it increases the paracellular Cl^- reabsorption through tight junctions.[5-11,19,20] On the other hand, WNK1 increases the activity of NCC, through inhibition of WNK4, and the activity of ENaC, and enhances the paracellular Cl^- reabsorption through tight junctions, whereas it decreases the activity of ROMK.[5,7-11,19,20]

In Gordon's syndrome, NCC and ENaC activity is enhanced, paracellular Cl^- reabsorption is further increased, and ROMK activity is further decreased,[5-11,13,19,20] leading to increased salt reabsorption and decreased potassium excretion, and therefore to hypertension and hyperkalemia, respectively,[5-8,10,11,14,19,20] Furthermore, the reduced potassium excretion is also due to the increased Na^+ reabsorption through NCC, which leaves less Na^+ to be exchanged for K^+ in more distal parts of the renal tubule via the conjugated functions of ENaC and ROMK, making the lumen less negative and

driving less K^+ in it through the already fewer ROMKs.[5-9,11,15,19-21] The lumen is also less negative due to the increased Cl^- reabsorption.[8,10] Additionally, the less negative lumen drives less H^+ in it, leading to reduced H^+ excretion, which in combination with hyperkalemia causes metabolic acidosis.[8,10,11] Finally, plasma renin values are low, because hypertension inhibits renin secretion,[7,8,11,14] and plasma and urine aldosterone values are usually normal, because low renin levels tend to lead to low aldosterone levels, whereas hyperkalemia tends to increase them.[5,6,8,10,11,20] Treatment with low doses of thiazide diuretics corrects all manifestations of Gordon's syndrome, because thiazides inhibit NCC, reducing salt reabsorption and leaving more Na^+ to be exchanged for K^+,[5,9,11,13,15] which is probably excreted through the flow-stimulated maxi-K channels.[6,8,20,21]

In our case, the patient demonstrated at the age of 11 hypertension, hyperkalemic hyperchloremic metabolic acidosis, low urinary potassium excretion, normal plasma aldosterone levels, normal creatinine clearance (normal renal function), and a relatively low rate of development, which set the diagnosis of Gordon's syndrome. Subsequently, he was effectively treated with chronic administration of low doses of hydrochlorothiazide (6.25 mg/12h) and dietary salt restriction. During his hospitalization after he had joined the army, the interruption of treatment resulted in low renal K^+ clearance and hyperkalemia, as K^+ gradually increased from 4.6 mEq/L on the first day to 5 mEq/L on the fifth day and FE_K decreased from 1.26% on the first day to 0.5% on the fifth day, and perhaps in a slight increase of blood pressure from 130/70 mmHg on the first day to 145/75 mmHg on the fifth day. These findings correspond with the already known great sensitivity of Gordon's syndrome to thiazide diuretics and indicate that its manifestations relapse when the treatment is discontinued. Nevertheless, the lack of a thiazide diuretic did not induce metabolic acidosis, because the interval was not long enough to disturb the acid-base balance and the hydrochlorothiazide administration restarted before serum K^+ levels exceeded the highest normal value. An interesting finding in this case is that nobody among his parents, his grandparents, his three siblings or any other relative had been diagnosed with this syndrome, although it is inherited in an autosomal dominant manner.[5-11] If any of his older relatives had any of the disease-causing mutations, he or she should already have manifested symptoms and/or clinical and laboratory findings of Gordon's syndrome, because its manifestations begin in childhood and all adults have hypertension and hyperkalemic hyperchloremic metabolic acidosis if they are left untreated.[10] Therefore, it is not illogical to assume that our patient might be a case of *de novo* gene mutation. However, the possibility of incomplete penetrance or variable expressivity cannot be excluded, because neither genotype nor phenotype analysis has been conducted on any of his relatives.

References

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005; 365: 217-223.
2. Viera AJ, Neutze DM. Diagnosis of secondary hypertension: an age-based approach. Am Fam Physician. 2010; 82: 1471-1478.
3. Seeman T. [Arterial hypertension in children and adolescents]. Cas Lek Cesk. 2006; 145: 625-32; discussion 632-634.
4. Mansia G, De Backer G, Dominiczak A, et al. 2007 ESH-ESC Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Blood Press. 2007; 16: 135-232.
5. San-Cristobal P, de los Heros P, Ponce-Coria J, Moreno E, Gamba G. WNK kinases, renal ion transport and hypertension. Am J Nephrol. 2008; 28: 860-870.
6. Kahle KT, Rinehart J, Giebisch G, Gamba G, Hebert SC, Lifton RP. A novel protein kinase signaling pathway essential for blood pressure regulation in humans. Trends Endocrinol Metab. 2008; 19: 91-95.
7. Huang CL, Kuo E, Toto RD. WNK kinases and essential hypertension. Curr Opin Nephrol Hypertens. 2008; 17: 133-137.
8. Xie J, Craig L, Cobb MH, Huang CL. Role of with-no-lysine [K] kinases in the pathogenesis of Gordon's syndrome. Pediatr Nephrol. 2006; 21: 1231-1236.
9. Cope G, Golbang A, O'Shaughnessy KM. WNK kinases and the control of blood pressure. Pharmacol Ther. 2005; 106: 221-231.
10. Gamba G. Role of WNK kinases in regulating tubular salt and potassium transport and in the development of hypertension. Am J Physiol Renal Physiol. 2005; 288: F245-252.
11. Kahle KT, Wilson FH, Lalioti M, Toka H, Qin H, Lifton RP. WNK kinases: molecular regulators of integrated epithelial ion transport. Curr Opin Nephrol Hypertens. 2004; 13: 557-562.
12. Riepe FG. Clinical and molecular features of type 1 pseudohypoaldosteronism. Horm Res. 2009; 72: 1-9.
13. Bonny O, Rossier BC. Disturbances of Na/K balance: pseudohypoaldosteronism revisited. J Am Soc Nephrol. 2002; 13: 2399-2414.
14. Landau D. Potassium-related inherited tubulopathies. Cell Mol Life Sci. 2006; 63: 1962-1968.
15. Chadha V, Alon US. Hereditary renal tubular disorders. Semin Nephrol. 2009; 29: 399-411.
16. von Vigier RO, Bianchetti MG. [Arterial hypertension in childhood and adolescence]. Ther Umsch. 1999; 56: 12-18.

17. Ardissino G, Edefonti A, Bianchetti MG, et al. [Diagnostic and therapeutic criteria of arterial hypertension in childhood]. G Ital Nefrol. 2006; 23: 149-162.
18. Luft FC. Mendelian forms of human hypertension and mechanisms of disease. Clin Med Res. 2003; 1: 291-300.
19. Huang CL, Cha SK, Wang HR, Xie J, Cobb MH. WNKs: protein kinases with a unique kinase domain. Exp Mol Med. 2007; 39: 565-573.
20. Huang CL, Yang SS, Lin SH. Mechanism of regulation of renal ion transport by WNK kinases. Curr Opin Nephrol Hypertens. 2008; 17: 519-525.
21. Rodan AR, Huang CL. Distal potassium handling based on flow modulation of maxi-K channel activity. Curr Opin Nephrol Hypertens. 2009; 18: 350-355.