**Case Report**

**Elevated plasma asymmetric dimethyl-L-arginine in a patient with Gordon syndrome**

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**Introduction**

Studies of rare genetic syndromes associated with arterial hypertension provide insight into factors affecting blood pressure and thus into the pathophysiology of essential hypertension (EH) [1]. Pseudo-hypoaldosteronism type II, also called Gordon syndrome or chloride shunt, is an autosomal dominant defect, combining volume-dependent salt-sensitive hypertension, hyperkalaemia, hyperchloraemia and metabolic acidosis associated with normal glomerular filtration rate and high responsiveness to thiazides and dietary sodium restriction, whereas plasma aldosterone is variable, being a net effect of low reninaemia and hyperkalaemia.

Gordon syndrome attracts a special attention because this set of features (hypertension, hyperkalaemia and acidosis) is usually caused by renal insufficiency, a relatively frequent cause of elevated blood pressure. Recently, the molecular basis of Gordon syndrome has been elucidated resulting from loss-of-function mutations within WNK (with no lysine kinase) type 4 (WNK4) and gain-of-function mutations of WNK type 1 (WNK1), with consequent loss of WNK4-mediated tonic inhibition of thiazide-sensitive sodium chloride cotransporter (NCCT) in the distal convoluted tubule, by a kinase-dependent mechanism [2]. As a consequence of increased NCCT activity, decreased sodium load reaching the collecting duct results in lower electrogenic sodium reabsorption and reduced tubular lumen electronegativity, a driving force for potassium and hydrogen secretion. Additionally, inactivating WNK4 mutations are also associated with lower activity of the renal outer medullar potassium channel (ROMK) in the collecting duct, due to the potentiated WNK4-dependent ROMK inhibition via clathrin-dependent endocytosis of ROMK independently of WNK4 kinase activity [3].

It is noteworthy that in Bartter and Gitelman syndromes, where opposite abnormalities are observed (decreased tubular sodium and chloride reabsorption, metabolic alkalosis, hypokalaemia, hypovolaemia with a tendency to lower blood pressure and hyper-reninaemia), various indices of nitric oxide (NO) generation and activity were elevated [4]. This was later linked to augmented expression of regulator of G protein signalling-2 (RGS-2) that terminates Gq protein-coupled receptor signalling, thus providing an inhibitory feedback mechanism against chronically elevated angiotensin II via raised NO bioavailability [4]. Moreover, excessive NO bioavailability might also reciprocally facilitate the proposed mechanism through the direct NO-dependent enhancement of RGS-2 activity [5]. Additionally, a Gordon syndrome subject and three Bartter syndrome patients exhibited opposite abnormalities in the secretion of atrial natriuretic peptide [6], a hormone using cyclic guanosine 3’,5’-monophosphate (cGMP) as an intracellular second messenger, similarly to NO.

Keeping in mind the relationship of cGMP-dependent pathways to blood pressure regulation and the tendency towards hypotension in Bartter and Gitelman syndromes, we hypothesized that hypertension in Gordon syndrome, a mirror of Gitelman syndrome, can be accompanied by abnormal NO activity. Impaired cGMP-mediated mechanisms may participate in excessive elevations of blood pressure in response to a high-salt diet, so-called salt-sensitivity, a feature of 50–75% of EH patients. This has been reported as inadequately low atrial natriuretic peptide levels [7] or reduced stable products of NO
metabolism, nitrate and nitrite (NOx) in plasma associated with elevated concentrations of an endogenous inhibitor of NO synthesis, asymmetric dimethyl-L-arginine (ADMA) [8] in salt-sensitive EH. We have previously demonstrated increased circulating ADMA levels in newly diagnosed untreated men with uncomplicated EH [9]. Therefore, we decided to measure plasma ADMA in a patient presenting with clinical features of Gordon syndrome.

Case report

A 48-year-old woman was admitted to our clinic because of resistant hypertension (treated with variable combinations of antihypertensive drugs) associated with electrolyte abnormalities. A history of hypertension was reported from the age of 21. Systolic blood pressure oscillated between 155 and 210 mmHg; diastolic blood pressure 105–120 mmHg. Funduscopic examination revealed grade III of hypertensive retinopathy. The remainder of the physical administration was normal.

The clearance of endogenous creatinine was within the normal range (91 ml/min per 1.73 m² of body-surface area). Serum sodium averaged 135–140 mmol/l (normal 138–147), whereas potassium and chloride levels were repeatedly elevated (potassium 5.5–5.8 mmol/l, normal 3.5–5.0; chloride 107–110 mmol/l, normal 95–105). Arterial blood gas analysis showed metabolic acidosis [pH 7.27–7.30; pCO₂ 27.2–34.6 mmHg; bicarbonate 12.3–16.8 mmol/l, normal 22–28; base excess (BE) between −8.5 and −12.8] and unchanged anion gap (12–15 mmol/l, normal 8–16). Results of other routine serum assays were normal.

Urine analysis showed no abnormalities; urine pH was 5.0–6.0. Since the patient’s urine pH spontaneously fell into 5.0, an ammonium chloride challenge was not performed. 24-h urinary excretion of potassium (28.8 mmol/day, normal 40–80 or >150 in the presence of hyperkalaemia) and fractional excretion of potassium (8.5%, normal 10–20) were lowered despite hyperkalaemia. Tall peaked T waves and episodic atrioventricular block grade I on ECG were recorded, being presumably due to high serum potassium. On chest X-ray aortic elongation was found. Cardiac ultrasound revealed moderate concentric left ventricular hypertrophy and mild left atrium enlargement. Abdomen ultrasound showed moderate hepatic steatosis. Renal arteriography demonstrated no abnormalities.

Plasma renin activity was suppressed: 0.1 ng angiotensin I/ml/h (normal 0.2–2.8) after the patient had been recumbent overnight and 1.3 ng angiotensin I/ml/h (normal 1.5–5.7) after the patient’s moving to an upright position. Plasma aldosterone concentrations were in the high–normal range: 140 pg/ml (normal 7.5–160) and 305 pg/ml (normal 35–310) for recumbent and upright position, respectively. Blood levels of cortisol (absolute values and circadian rhythm), thyroid-stimulating hormone, free thyroxin, free triiodothyronine as well as 24-h urinary excretion of metanephrine, normetanephrine, vanilmandelic acid and 5-hydroxyindoloacetic acid were normal.

Oral administration of hydrochlorothiazide (25–50 mg/day) for 2 weeks corrected metabolic acidosis (pH 7.39; pCO₂ 40.6 mmHg; bicarbonate 24.3 mmol/l; BE −0.1) and resulted in normalization of blood pressure (130/80 mmHg), serum potassium (4.1 mmol/l) and chloride (103 mmol/l).

A family survey revealed elevated blood pressure in the patient’s only brother, aged 50 (140/100 mmHg) and in her two sons aged 27 and 29 (150/90 and 145/105 mmHg, respectively). The patient’s brother also exhibited hyperchloraemia (108 mmol/l), compensated metabolic acidosis (pH 7.42; pCO₂ 29.5 mmHg; bicarbonate 18.9 mmol/l; BE −4.1) and serum potassium of 4.3 mmol/l. Abnormal serum biochemistry in the patient’s sons included exclusively serum chloride at the upper limit of the normal range (105 mmol/l) in one of the two sons. The other son exhibited mild mental impairment of unknown origin since early childhood. A history of hypertension in both parents of the patient was also recorded.

Dimethyl-L-arginine assay

After an overnight fast, blood was drawn from an antecubital vein and collected into pre-chilled tubes containing ethylenediaminetetraacetic acid and plasma was separated and frozen in −80°C until assayed. ADMA and its biologically inactive stereoisomer symmetric dimethyl-L-arginine (SDMA) were analysed by high-performance liquid chromatography as previously described [10].

In our Gordon syndrome patient, ADMA level was elevated to 1.9 μmol/l with the reference to 20 healthy volunteers (mean ± SD 0.9 ± 0.2 μmol/l, range 0.6–1.3) aged 45 ± 9 years (range 20–59). SDMA level was unchanged (1.1 μmol/l) as compared with the control group (1.0 ± 0.3 μmol/l, range 0.4–1.6). Conditions (other than hypertension) known to be associated with elevated plasma ADMA (hyperlipidaemia, hyperhomocystinaemia, diabetes mellitus and obesity) had been excluded.

Comments

Differential diagnosis

In the present case, normal creatinine clearance allowed the exclusion of renal insufficiency, the common cause of the constellation (hypertension, hyperkalaemia, metabolic acidosis) found in our patient. Another relatively frequent cause (hyporeninaemic hypoaldosteronism with sodium retention in the course of diabetic nephropathy or administration of classical non-steroidal antiinflammatory drugs or coxibs) was also absent. Among Mendelian forms of human hypertension [glucocorticoid-remediable
aldosteronism (GRA), Liddle syndrome, apparent mineralocorticoid excess, gain-of-function mineralocorticoid receptor mutation, Gordon syndrome) that are associated with low reninaemia, solely patients with GRA and Gordon syndrome exhibit the lack of plasma aldosterone suppression [1], as in our subject. However, GRA is associated with hypokalaemia and metabolic alkalosis, whereas the opposite was the case in our patient, making Gordon syndrome probable. The high-normal aldosterone levels were likely to result from the domination of direct hyperkalaemia-mediated stimulation of aldosterone generation over low renin-dependent inhibition of aldosterone release. This allowed exclusion of aldosterone deficiency, yet the impaired responsiveness to mineralocorticoids should still have been taken into account in differential diagnosis. The lack of predisposing conditions, i.e. obstructive nephropathy, analgesic nephropathy, chronic pyelonephritis, renal amyloidosis, systemic lupus erythematosus, sickle cell anaemia, intake of triamterene, amiloride or spironolactone [11], argues against this possibility. Loss-of-function mutations affecting the mineralocorticoid receptor or the epithelial sodium channel are responsible for autosomal dominant and recessive forms of pseudohypoaldosteronism type I, respectively—which—in addition to hyperkalaemia and metabolic acidosis—presents with salt wasting and hyperreninaemia as opposed to salt-sensitive hypertension and renin suppression in Gordon syndrome. Additionally, the presence of typical biochemical abnormalities in the available family members and the effectiveness of a thiazide support the diagnosis of Gordon syndrome, an autosomal dominant defect.

Elevated ADMA in Gordon syndrome

Unchanged circulating concentrations of SDMA, whose unique route of elimination is renal excretion, could be expected in a subject with normal creatinine clearance, as in our Gordon syndrome patient. Marescau et al. [12], who studied 135 non-dialysed subjects with varying degrees of chronic renal insufficiency, demonstrated comparable (about 2-fold) rises of serum ADMA in patients with creatinine clearance below 10 ml/min, whereas in earlier stages of chronic kidney disease, mainly SDMA concentrations were increased with progressive elevations of the SDMA to ADMA ratio with decreasing creatinine clearance. Selective rise of plasma ADMA with normal SDMA might be a consequence of augmented methylation of arginine residues within proteins by protein arginine type I N-methyltransferases and/or diminished ADMA degradation by dimethylarginine dimethylamino-hydrolase (DDAH). Interestingly, oxidative stress both stimulates expression of protein arginine type I N-methyltransferases [13] (which preferentially catalyse ADMA formation) and negatively regulates DDAH activity [14] (which governs the majority of ADMA catabolism but is unable to decompose SDMA). Since indices of reactive oxygen species formation were depressed in Bartter and Gitelman syndromes with consequent impairment of angiotensin II-mediated responses [15,16], a hypothetically increased oxidative stress might offer a plausible explanation for elevated ADMA in Gordon syndrome, a mirror of Gitelman syndrome.

The clinical significance of ADMA accumulation in Gordon syndrome, if confirmed by a larger study, remains to be clarified. There is some evidence that elevated ADMA production contributes to impaired NO release and augmented blood pressure rises on high-sodium diet in salt-sensitive EH, as suggested by Fujiwara et al. [8], who measured ADMA and NOx in plasma at different levels of dietary sodium intake in EH. However, available human studies do not allow to definitely attach consequences of NO deficiency or excess to specific sites of NO action. In healthy volunteers, Facchini et al. [17] based their conclusion concerning a link between NO formation and blood pressure changes in response to a high-sodium diet on the measurement of urinary NOx, an index of the whole-body NO formation. NO not only continuously regulates peripheral vascular resistance but also affects extracellular fluid volume regulation in the kidney. That regulation of NO formation might vary between different tissues, as can be supposed from an article by Matsuoka et al. [18], who observed elevated urinary ADMA and low urinary NOx in salt-sensitive Dahl rats fed on a high-salt diet with no differences in plasma NOx and ADMA. Indeed, Higashi et al. [19] reported an impaired ability of intravenous L-arginine to produce renal vasorelaxation in salt-sensitive EH subjects on a high-salt diet as compared to a low-salt diet, with no differences in blood pressure responses to L-arginine. Moreover, a human study revealed the ability of low doses of intravenous ADMA to increase renovascular resistance and lower urinary sodium excretion without detectable effects on blood pressure in healthy volunteers [20]. Keeping in mind the recently reported dependence of ambulatory blood pressure in the general population on polymorphisms within the WNK1 gene [21], known to be related to Gordon syndrome, a potential role of NO-dependent pathways in blood pressure regulation at different levels of dietary sodium intake may be a topic of future research, focused on subjects with rare monogenic forms of hypertension as well as on their mildly affected relatives frequently misdiagnosed as EH.

Conflict of interest statement. None declared.

References

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