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Familial Mineralocorticoid Induced Hypertension in the Sultanate of Oman

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ارتفاع ضغط الدم الوراثي الناتج عن القِشْرانِيَّات المَعْدِنِيَّة في سلطنة عمان

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الملخص: الهدف: وجدنا في دراسة سابقة عددا كبيرا من المرضى العمانيين المصابين بارتفاع ضغط الدم الوراثي والذين استجابوا لعقار سبايرونولاكتون ، وهو عقار يبطل وظيفة مستلمات القِشْرانِيَّاتُ المَعْدِنِيَّة الموجودة فوق الكلى . وهذا يدل على ارتفاع انتشار ضغط الدم الناتج عن القشرانيات المعدنية. نريد في هذا البحث إثبات ارتفاع نسبة هذا النوع من ضغط الدم العالي عند العمانيين الذين لديهم تأريخ عائلي موجب لذلك المرض. **الطريقة:** تم قياس مستويات أملاح الكالسيوم والبوتاسيوم والكرياتنين ، وكذلك هرموني الرينين والالدوستيرون عند كل المرضى . بالإضافة إلى عمل تفريسة بطنية فائقة الصوت للغدة الكظرية والكلى في كل المرضى وعمل تَصْويرٌ مَقْطَعِيٌّ مُحَوسَب في 4 مرضى. **النتائج:** وجدنا في هذه الدراسة الصغيرة نسبة عالية من المرضى 18 من مجموع 27 (66 %) لديهم مستوى رنين غير محسوس (منخفض) مع مستوى طبيعي لهرمون الدوستيرون (14 مريضا) واستجابوا لعقار سبايرونولاكتون. **الخلاصة:** من هذه الدراسة نتوقع كثرة انتشار ارتفاع نسبة ضغط الدم الوراثي في الشرق الأوسط ، وأن القدرة على الحفاظ على الملح في الجو الحار ربما يعطي ميزة نوعية من أجل البقاء.

مفتاح الكلمات: ارتفاع ضغط الدم، العائلي، القِشْرانِيَّاتُ المَعْدِنِيَّة، انتشار عالي، عمان.

Objectives: In Oman, many hypertensive patients with a family history of the disease respond to treatment with spironolactone, a mineralocorticoid receptor (MC-R) blocking agent thus suggesting a high prevalence of mineralocorticoid (MC) induced disease. The aim of this study was to document the prevalence of MC induced disease in patients with a positive family history of hypertension (HTN). ***Methods:*** Serum calcium, potassium, creatinine, aldosterone and renin levels were measured under standard conditions in all patients together with an abdominal ultrasound scan and an adrenal computed tomography (CT) scan in four patients. ***Results:*** In this small study, we show that 18 of the 27 patients (66%) had undetectable (suppressed) renin levels with usually normal aldosterone values (14 patients) and respond to treatment with spironoactone. ***Conclusion:*** We suggest that MC induced hypertension is likely to be common in the Middle East. In evolutionary terms, this makes sense as the ability to conserve salt in hot climates might be expected to confer a definite survival advantage.

Key words: Hypertension, familial; Mineralocorticoids; High prevalence; Oman

Advances in Knowledge

- *This is the first study uniquely selecting patients with familial hypertension*
- *Mineralocorticoid induced hypertension is reported in 10% or more of the general hypertensive population. We have only studied patients with a positive familial history of the disease and found a much higher prevalence (66%) with mineralocorticoid (MC) induced disease*

Application to Patient Care

- *Patients with a positive family history of hypertension should undergo a short one month trial of a mineralocorticoid blocking drug such as spironolactone.*

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It has generally been recommended[1-2] that screening for hyperaldosteronism be considered at least for hypertensive patients with spontaneous hypokalemia (K <3.5 mmol/L), or with marked diuretic-induced hypokalemia (K <3.0 mmol/L), with hypertension refractory to treatment with three or more drugs or those found to have an incidental adrenal adenoma. Previously, primary hyperaldosteronism (PAL) was not believed to be familial and thought to account for less than 1% of hypertensive patients and hypokalemia was considered a prerequisite for pursuing diagnostic tests[2]. Recent studies with screening of both hypokalemic and normokalemic hypertensives have reported now a much higher prevalence of this disease, with primary hyperaldosteronism accounting for up to 12% of hypertensive patients most of them being normokalemic.[3-4] Furthermore, in 1991, a second form of familial hyperaldosteronism (FH-II) that was not glucocorticoid remediable was first reported. There were six patients, four with aldosterone-producing adenoma (APA) and two with bilateral adrenal hyperplasia (BAH)) among three families.[5] Till 2001, a total of 68 patients among 27 families have been described, making FH-II more common than FH-I (34 patients among five families).[6] To date, two familial forms of hyperaldosteronism have been identified: glucocorticoid suppressible, familial hypertension Type 1 (FH1) and glucocorticoid non-suppressible disease, (FH2).[6-7]

We recently reported a potentially high prevalence of familial mineralocorticoid (MC) induced hypertension (HTN) in patients attending our general endocrine clinics[8] and found that in 39 of 45 patients (80 %) their blood pressure could be controlled using spironolactone alone. We therefore concluded that the prevalence of MC induced disease in Oman might prove to be quite high[8]. In the UK, a recent study of more than 800 hypertensive patients in a general practice setting, who were without a positive family history, revealed that 14% responded to spironolactone with a fall in BP of 26/11 mmHg. All of them had suppressed renin levels, but as in our study, the aldosterone levels were only occasionally raised.[9] Only 1 of these patients had Conn's syndrome. We are now providing a more detailed account of 27 additional subjects with familial disease, but in addition their circulating renin and aldosterone levels were measured before starting treatment with spironolactone.

METHODS

These 27 hypertensive patients were from different families having one or more affected parents and siblings, twenty four were Omanis and three Sudanese. They had been randomly selected from our general endocrine clinics if they had a positive family history of hypertension. Serum calcium, potassium, creatinine, aldosterone (n. 28-440 pmol/L) and renin (n. 2.4-21.9 ng/L) levels were measured after lying supine for 6 hours and after stopping β-blockers under supervision for 4 days.[10] Renal ultrasounds were obtained in all patients, as well as a contrast adrenal computed tomography (CT) scan, with 2-3mm slices, in those with documented hyperaldosteronism and suppressed renin levels. The patients with suppressed renin levels were given a 1 month course of spironolactone 50-100 mg daily alone to four newly diagnosed patients, or in addition to other antihypertensives in the remainder. These were on a minimum of two drugs (16 patients) or ≥ three drugs (7 patients). The usual combination of medications was angiotensin-converting enzyme (ACE) inhibitors, angiotensin II (AT2) receptor blockers, diuretics or beta-blockers (4 patients). No patients were taking methyldopa or clonidine. If the blood pressure (BP) was controlled (<140/80), after 2-4 weeks the other medications were sequentially withdrawn at weekly intervals until the patient was taking spironolactone alone for at least one month. Renin was measured using a renin immunoradiometric assay (IRMA) kit (DSL-25100) from Diagnostic Systems Laboratories Inc. and aldosterone was measured via radioimmunoassay (RIA) kit from Dia Sorin Inc. The normal ranges used are from the North American data provided by the relevant companies. Formal suppression tests of aldosterone secretion were not performed. Fully informed consent was obtained from all patients. There was no conflict of interest financial or otherwise.

RESULTS

Of the 27 patients studied, renin levels were suppressed in 18 (66%), but aldosterone values were normal in 13, elevated in 4 and undetectable in one case. The remaining 9 patients had normal values of aldosterone, but renin levels were low in 3 of them [Table 1]. Of the 18 patients with suppressed renin levels, 14 were available for follow up whilst taking spironolactone and in 1 other case taking moduretic. Their final median BP was 130/70 with a range of 140/70-100/70.

Table 1: ***Data from 27 patients with familial hypertension. The median basal blood pressure of the 4 patients not on medication was 155/105, with a range of 170/95 – 150/110 (patients 1, 3, 10, 17). Basal blood pressure values of patients already on treatment are not shown as they were only slightly elevated.***

Patient No	Age	Sex	Renin ng/L	Aldosterone pmol/L	Final BP
1	45	F	<0.5	380	125/70
2	49	M	<0.5	140	125/70
3	56	F	<0.5	57	130/70
4	44	F	<0.5	112	130/70
5	55	M	<0.5	168	LTFU
6	45	M	<0.5	225	LTFU
7	44	F	<0.5	70	125/70
8	58	M	<0.5	108	100/70
9	42	F	<0.5	227	LTFU
10	58	F	<0.5	220	135/85
11	51	F	<0.5	40	LTFU
12	46	F	<0.5	136	135/70
13	42	M	<0.5	351	130/80
14	44	F	<0.5	<20	130/75
15	56	F	<0.5	575	140/70
16	42	F	<0.5	508	120/70
17	69	F	<0.5	543	130/80
18	49	M	<0.5	500	120/70
19	48	F	2.3	407	LTFU
20	42	F	0.5	321	130/70
21	38	F	1.3	323	110/75
22	36	M	2.7	79	150/85
23	39	F	2.5	140	145/85
24	54	M	4.7	383	155/90
25	45	M	3.1	381	150/80
26	42	M	2.6	300	140/80
27	50	F	20	448	145/80
Normal range Supine > 6 hrs			2.4-21.9	28-440	

Serum calcium and potassium levels were normal in every patient. Serum creatinine levels were mildly elevated in two cases at 129 and 147 μmol/L [Table 1]. There were 5 patients in consanguineous marriages in this group.

DISCUSSION

The results of this study further support our original suggestion[8] that there is a high prevalence of MC induced HTN in patients who have a strong family history of the disease. Two thirds of our patients in this study had suppressed renin levels with autonomous

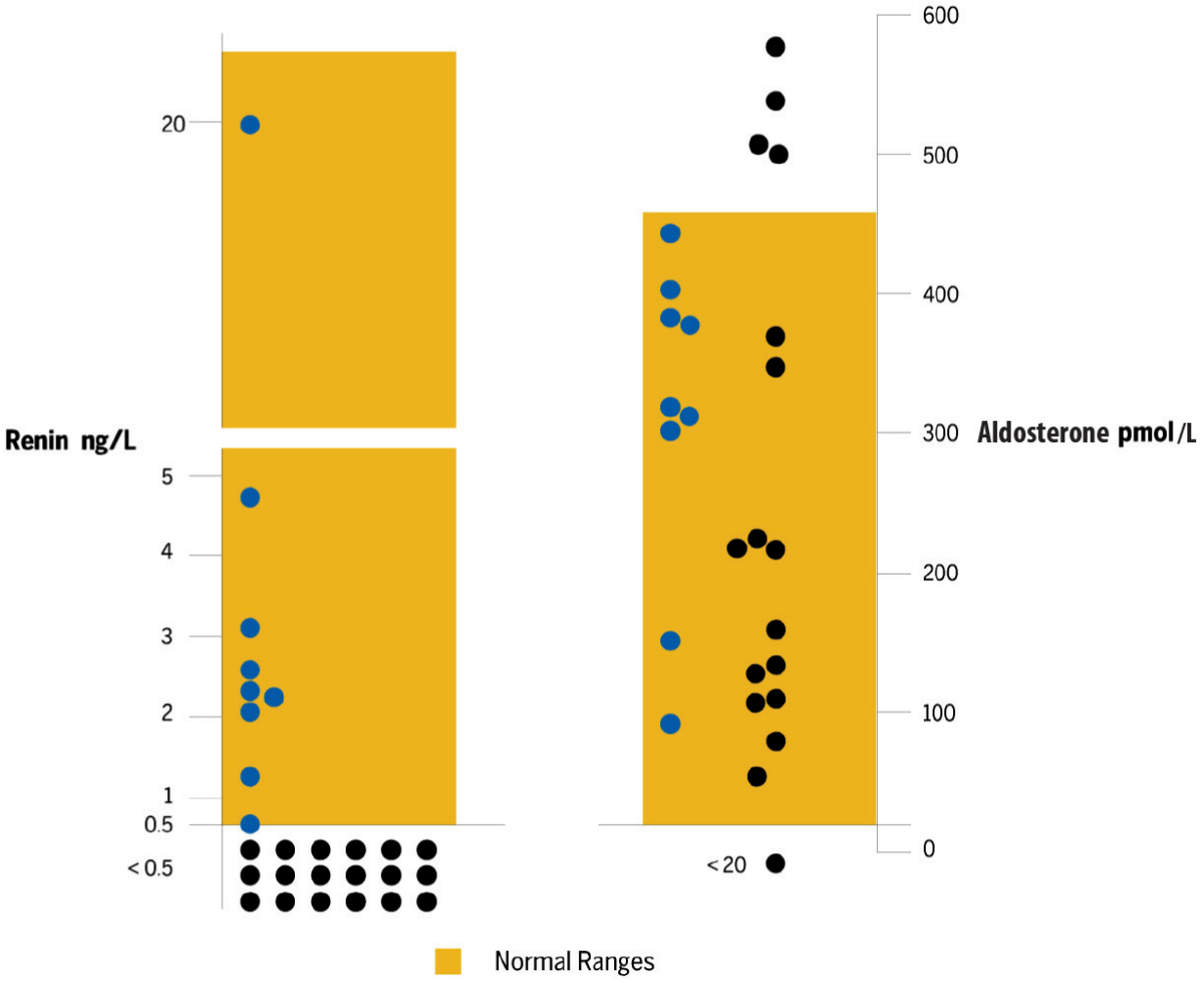

Figure 3: ***Shows aldosterone values in patients with supressed (◆) normal renin (◆) levels***

aldosterone production, and their BP was controlled using spironolactone a known MC receptor blocking agent. It is now recognized that primary aldosteronism occurs in more than 10 percent of the general hypertensive population and that hypokalaemia is an uncommon presenting feature.[3-9] In fact, of the 72 patients with familial disease we have studied so far, only 6 were hypokalaemic at presentation including the one patient with Conn's syndrome.[8] We did not carry out dexamathasone suppression tests in these patients, but suspect that the majority have FH2 as we earlier found only one responsive family in 15 that were tested. The pathophysiology of FH2 is not known with certainty, but presumably results from one or more activating mutations in the renin/angiotensin/aldosterone pathway. Of interest is the one patient who had suppressed renin and aldosterone levels. This combination occurs in Liddle's syndrome and apparent mineralocorticoid excess (AME). Both result from excessive renal tubular reabsorption of sodium; the former caused by activating mutations of the epithelial sodium channels (ENaC) and the latter activation of the type I MC-receptor. In AME there is an inherited or acquired deficiency of the renal isoform of 11-b-OH steroid dehydrogenase (11-b-OH SD). Normally this enzyme converts cortisol to inactive cortisone. In its absence, tissue cortisol levels increase activating the MC-receptor. Our patient does not have Liddle's syndrome, however, as this disorder does not respond to a MC-receptor blocking drug. AME is also unlikely as there is no history of childhood ill health hypokalemia or ingestion of compounds known to inactivate 11-b-OH SD such as liquorice or chewing tobacco. We are currently exploring the possibility that she might be secreting another MC-receptor stimulating compound.

The Brisbane group has suggested that FH-II (familial hypertension type 2) has an autosomal dominant mode of transmission with linkage to 7p22 and gender distribution that is roughly equal.[6-11] However, apart from being familial, FH-II has no specific clinical, biochemical or morphological hallmarks that permit distinction from apparently non-familial PAL, with the two groups demonstrating similar mean ages, gender distributions, hypokalaemic percentages, mean upright plasma aldosterone and PRA levels, with these and the use of other investigative techniques.[10] This suggests that the genetic defects that underlie the development of FH-II may also be operative in many patients with apparently non-familial PAL and may be picked up earlier by family screening.

Indeed, it has been suggested that PAL passes through four phases in its evolution: low renin normotension, normokalemic primary aldosteronism and finally hypokalemic primary aldosteronism.[12]

CONCLUSION

MC induced disease seems to be common in Oman. In evolutionary terms this makes sense as the ability to conserve salt in hot climates might be expected to confer a definite survival advantage. We recommend that all patients with a positive family history of HTN should be screened for MC induced disease or at least receive a short therapeutic trial of spironolactone to avoid unnecessary complications.

To our knowledge there have been no previous reports documenting MC induced disease in patients screened using a positive family history only.

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