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Glucocorticoid Remediable Aldosteronism: Low Morbidity and Mortality in a Four-Generation Italian Pedigree

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Glucocorticoid remediable hyperaldosteronism (GRA) is a monogenic form of inherited hypertension caused by a chimeric gene originating from an unequal cross-over between the 11 β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) genes. GRA is characterized by high plasma levels of aldosterone (regulated by ACTH) with suppressed plasma renin activity and the production of two rare steroids, 18hydroxycortisol and 18oxocortisol. Affected patients usually show severe hypertension and an elevated frequency of stroke at a young age. Affected women have a high risk of developing preeclampsia during pregnancy.

Here, we describe a 5-generation pedigree from Sardinia in which the presence of the chimeric gene is demonstrated in 4 generations. This family displays a mild phenotype with average blood pressure levels of 131/86 mm Hg for GRA+ patients. The occurrence of stroke is very low, and preeclampsia was not observed in 29 pregnancies from 8 GRA+ mothers. We investigated whether the cross-over site (between the CYP11B1 and CYP11B2 genes) or biochemical characteristics could explain this phenotype. The cross-over site was located at the end of intron 3, in the same region as described in other families.

We found a significant correlation between blood pressure and 18hydroxycortisol, 18oxocortisol, and plasma aldosterone levels, but not with kallikrein. However, none of the biochemical or genetic parameters investigated could explain the mild phenotype of the family. (*J Clin Endocrinol Metab* 87: 3187–3191, 2002)

GLUCOCORTICOID REMEDIABLE HYPERALDOSTERONISM (GRA) is a monogenic form of inherited hypertension first described by Sutherland *et al.* (1). This disease is characterized by high plasma aldosterone levels (PAL), suppressed plasma renin activity (PRA) (2), and the production of two rare steroids, 18-hydroxycortisol (18OHF) and 18-oxocortisol (18oxoF). The synthesis of these steroids requires the simultaneous presence of a 17α-hydroxylase activity and the two C18 (18-hydroxylase and 18-oxidase) activities typical of the CYP11B2 (aldosterone synthase) enzyme (3, 4). In GRA, the secretion of aldosterone is primarily regulated by ACTH rather than angiotensin II (5); in fact, the symptoms are exacerbated by ACTH administration and normalized by glucocorticoid administration. Despite the state of hyperaldosteronism, hypokalemia is not a common feature (6).

The GRA is inherited in an autosomal dominant fashion and is caused by the presence of a chimeric gene originating from an unequal cross-over between the CYP11B1 (11β-hydroxylase) and CYP11B2 genes (7). The hybrid gene has CYP11B1 sequences at the 5′ end, including the promoter, and CYP11B2 sequences at the 3′ end (7–9). The presence of the CYP11B1 promoter ensures the expression of the hybrid gene throughout the adrenal cortex, whereas the sequences of CYP11B2 lead to the inappropriate synthesis of aldosterone, 18OHF, and 18oxoF. The cross-over site occurs between intron 2 and exon 4, in agreement with the finding that sequences of CYP11B2, encoded by exons 5 and 6, are required for aldosterone, 18OHF, and 18oxoF production (10, 11). However, the exact position of the cross-over site between intron 2 and exon 4 does not seem to affect the phenotype (12, 13).

GRA is diagnosed by demonstrating the presence of the chimeric gene by a long PCR-technique and/or by a Southern blot (7, 11, 14); the dexamethasone suppression test (DST) (1, 15) has been shown in two recent reports to be unspecific for the diagnosis of GRA (16, 17).

In affected families, there is an increased frequency of early death from stroke (18, 19) and an increased risk for an exacerbation of hypertension during pregnancy (20). Despite severe hypertension being a frequent feature of these patients, families have been described with members with mild hypertension or with normotensive individuals (21). Dluhy *et al.* (13) reported that blood pressure (BP) in different affected kindreds was not correlated to the degree of hyperaldosteronism, the urinary sodium excretion, or to the production of 18OHF and 18oxoF. However, families with lower kallikrein secretion had higher BP levels (13). In a recent study, the severity of hypertension was reported to be related to the gender and the degree of biochemical disturbance (22); the maternal origin of the chimeric gene has been related to

Abbreviations: BMI, Body mass index; BP, blood pressure; DBP, diastolic blood pressure; DST, dexamethasone suppression test; GRA, glucocorticoid remediable hyperaldosteronism; 18OHF, 18hydroxycortisol; 18oxoF, 18oxocortisol; PAH, pregnancy-aggravated hypertension; PAL, plasma aldosterone levels; PE, preeclampsia; PRA, plasma renin activity; SBP, systolic blood pressure.

a higher mean arterial pressure by some authors (12) but not by others (22).

Here, we describe a five-generation pedigree in which the presence of the chimeric gene is demonstrated in four generations; this kindred shows a particularly benign phenotype, with a high number of affected members who are normotensive or mildly hypertensive and a very low frequency of stroke.

Subjects and Methods

Family screening

The relatives of the proband were contacted for clinical and biochemical tests and were screened for GRA after giving informed consent (Fig. 1). The evaluations included a medical history; three BP determinations, performed according to the suggestions of the Joint National Committee VI; a 24-h urine collection for creatinine, kallikrein, 18OHF, and 18oxoF measurements; blood sampling for the measurement of potassium, creatinine, PRA, PAL, and cortisol between 0800 and 0900 h; and the DST, performed as described previously (1, 15, 16). Plasma cortisol suppression (*i.e.* <28 nM) was used as an index of dexamethasone effect. The patients were on a self-selected diet at the time of screening. All the patients were in wash-out from all antihypertensive drugs for at least 3 wk, and none were taking glucocorticoids. Past medical records and the death certificate were reviewed for patient III-3.

Laboratory evaluation

Potassium, creatinine, PAL, PRA, and cortisol were measured as described previously (16). Urinary 18OHF and 18oxoF were measured using an ELISA method (23, 24). Urinary kallikrein was kindly measured by Dr. Paolo Madeddu (Sassari, Italy) as reported previously (25).

Long-PCR for the amplification of the chimeric gene and Southern blotting of genomic DNA were performed as described previously (11, 16).

Statistics

Cumulative data are expressed as mean ± SD. Unpaired *t* tests were used to compare affected and unaffected family members. Correlations between variables were evaluated with Spearman's correlation coefficient. Stepwise multiple regression analysis was used to examine which of the selected variables had a statistical influence on BP. The α level for entry and removal of terms at each forward step was 0.15.

Results

Proband's case report

The proband (patient III-5) is a 51-yr-old white woman originating from Sardinia, seen for hypertension stage 2 at our Hypertension Unit. She had been hypertensive for 1 yr and was treated with amlodipine (10 mg/d). Home and office BP levels ranged from 135–150/90–100 mm Hg. Po-

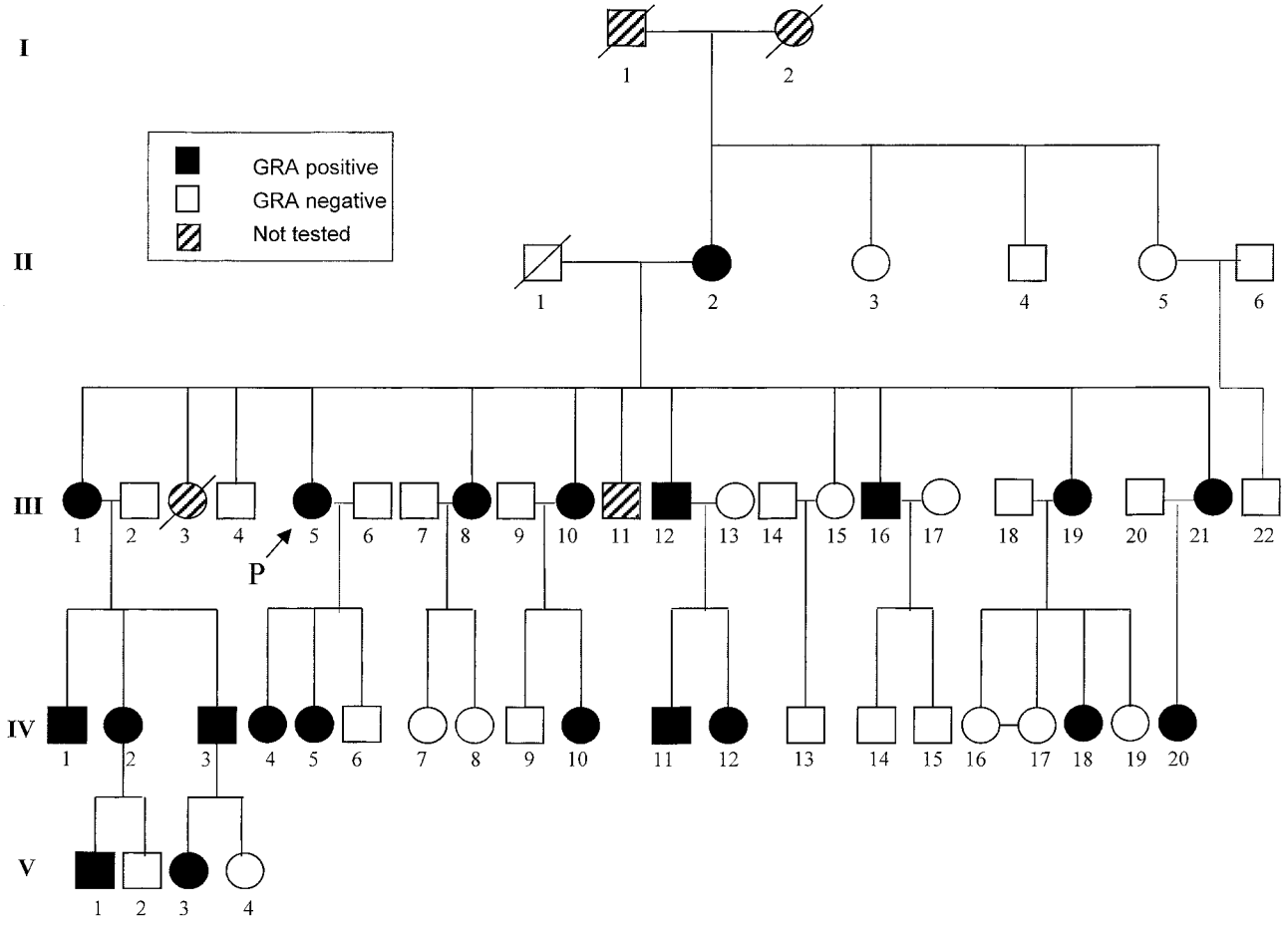

FIG. 1. Pedigree structure of the GRA-affected family. Females are designated by *circles*, and males by *squares*. Affected status is indicated by *blackened symbols*. A *diagonal line through the symbol* indicates deceased individuals. Patients I-1, I-2, III-3, and III-11 (*shaded symbols*) were not tested.

TABLE 1. Comparison of clinical and laboratory data in the GRA+ and GRA− members of the family (expressed as mean ± SD)

Parameter	Normal values	GRA+ n = 21	GRA− n = 18	*P*
Age (yr)		35.5 ± 18.1	31.8 ± 22.3	0.36
Sex (male/female)		6/15	9/9	
Systolic blood pressure (mm Hg)	<140	131 ± 34	110 ± 21	0.06
Diastolic blood pressure (mm Hg)	<90	86 ± 20	69 ± 14	0.07
BMI (kg/m^2)	20–25	23.4 ± 3.4	21.8 ± 5.5	0.03
PAL (pmol/liter)	137–832	534.5 ± 109.3	300.7 ± 117.6	0.7
PRA (ng/liter)	0.40–1.62	0.06 ± 0.07	0.47 ± 0.35	0.006
PAL/PRA	<5200	8622 ± 1518	640 ± 336	<0.0001
Urinary 18oxoF (nmol/d)	0.5–3.9	221.6 ± 479.6	2.3 ± 2.2	<0.0001
Urinary 18OHF (μmol/d)	0.05–0.29	1.85 ± 0.64	0.1 ± 0.04	<0.0001
Urinary kallikrein (UI/g creat)	0.47–1.09	0.98 ± 0.44	0.78 ± 0.56	0.26
Potassium (mM)	3.5–5.0	4.3 ± 0.4	4.2 ± 0.3	0.8
Plasma cortisol (nM)	110–520	343 ± 133	354 ± 152	0.79
PAL post DST	>110	69 ± 11	275 ± 941	<0.0001

tassium level was 4.1 mM; upright PRA was suppressed (0.027 ng/liter), and upright aldosterone levels were increased (859.9 pM). Primary aldosteronism was confirmed by the saline infusion test. DST and long-PCR indicated the diagnosis of GRA, which was confirmed by Southern blot analysis.

The pedigree for the proband's large family (54 members) was traced through 5 generations. A total of 39 members of 4 generations were screened for GRA (Fig. 1); 21 patients resulted positive.

Clinical data

Systolic BP (SBP) levels of at least 140 mm Hg and/or diastolic BP (DBP) levels of at least 90 mm Hg were found in 8 of 21 (38.1%) GRA+ patients; for subjects aged less than 18 yr, BP levels were considered as normal below the 95th percentile for the age, as suggested by the Task Force on BP control in children (26). Four of 18 (22.2%) GRA− subjects had high BP levels. Furthermore, in the GRA+ group, only 3 of 21 developed hypertension before the age of 36 yr and only 1 patient before the age of 24 yr. No patients, to date, developed hypertension before the age of 18 (Tables 1 and 2).

The differences in BP levels between GRA+ and GRA− were only marginally significant ($P = 0.06$ for SBP, and $P = 0.07$ for DBP) (Table 1). Only 1 subject (III-3) had a cerebrovascular event [1 of 43; 1 of 22 (4.5%) between the GRA+ if we consider the patient as probable GRA+]. She died at the age of 33 because of a subarachnoid hemorrhage. Her GRA status is unknown, but she had been normotensive until the event. Subjects I-1 and I-2 died at ages of more than 75 yr, 1 of pneumonia and the other of cancer.

Twenty-nine pregnancies had occurred in this family from 8 GRA+ mothers. There were no cesarean sections in this group of pregnancies. The data from the prenatal and hospital records of 17 pregnancies from GRA+ mothers showed no pregnancies with transient hypertension. Chronic hypertension was reported in 1 pregnancy, but no pregnancy-aggravated hypertension (PAH, defined as an increase of at least 30 mm Hg in SBP or at least 15 mm Hg in DBP, from baseline BP ≥ 140/90 mm Hg before pregnancy) was reported. No pregnancies were complicated by preeclampsia (PE). The average birth weight was 3250 g for the infants with GRA+ mothers and 3200 g for the infant with a GRA− mother.

TABLE 2. Occurrence of clinical and biochemical abnormalities in patients GRA+ and GRA−

	Occurrence in GRA+	Occurrence in GRA−
Number of subjects	21/39 (53.8%)	18/39 (46.2%)
Hypertension	8/21 (38.1%)	4/18 (22.2%)
Hypokalemia	0/21 (0%)	0/18 (0%)
Elevated PAL	1/21 (4.7%)	0/18 (0%)
Suppressed PRA	20/21 (95.2%)	1/18 (5.5%)
Elevated PAL/PRA ratio	17/21 (80.9%)	1/18 (5.5%)
Elevated urinary 18oxoF	21/21 (100%)	1/18 (5.5%)
Elevated urinary 18OHF	21/21 (100%)	0/18 (0%)
Stroke[a]	1/22 (4.5%) or 0/21 (0%)	0/18 (0%) or 1/19 (5.3%)
Pre-eclampsia	0/29 (0%)	0/1 (0%)
PAH	0/29 (0%)	0/1 (0%)
DST positive	21/21 (100%)	0/18 (0%)

u18OHF, Urinary 18-hydroxycortisol; u18oxoF, urinary 18-oxocortisol.

[a] The frequency of stroke in the two subgroups of patients depends on the unknown genotype of patient III-3, who is the only one who died for stroke.

Laboratory data

None of the patients of this pedigree had potassium levels below 3.6 mM (Tables 1 and 2); potassium levels were not significantly different between the GRA+ group and the GRA− group. Upright PAL was not statistically higher in the GRA+, compared with GRA−. In contrast, PRA was significantly lower ($P = 0.006$) and the PAL/PRA ratio higher ($P < 0.0001$) in the GRA+ group. Also, 18OHF and 18oxoF were significantly higher in the GRA+ group, compared with the GRA− group, without any overlap ($P < 0.0001$) except for patient Iv-8, who displayed slightly high levels of 18oxoF despite being GRA−; however, the levels of 18OHF were within the normal range. All the GRA+ patients, but not the GRA− patients, displayed a reduction of the PAL to below 110 pM after DST. Urinary kallikrein tended to be higher in our family, compared with a group of 31 normal volunteers and with a group of 48 essential hypertensives, both coming from the same region as the family (25); however, the kallikrein values were not significantly different between GRA+ and GRA−.

We found a significant positive correlation between 18OHF and 18oxoF levels ($P < 0.0001$). Moreover, urinary levels of 18OHF and 18oxoF were correlated with PAL ($P =$

0.0003 and $P = 0.0002$, respectively) but not with age. No significant correlations were found between kallikrein levels and other variables.

Stepwise multiple regression analysis was also performed to examine which, between selected independent variables [age, sex, body mass index (BMI), upright PAL, urinary 18OHF, 18oxoF, and kallikrein], could predict BP levels (Table 3). Both age and urinary 18OHF levels were strong predictors of SBP and DBP.

Genetic data

After demonstrating the presence of the chimeric gene, by long-PCR and Southern blotting, we analyzed the site of the cross-over between CYP11B1 and CYP11B2. The sequencing of the chimeric PCR product demonstrated that the cross-over site was located at the end of intron 3, just before the beginning of exon 4 (data not shown).

Discussion

GRA is a monogenic form of hyperaldosteronism characterized by particular clinical and laboratory findings. We describe here a family originating from Sardinia that displays different clinical characteristics, compared with those of published families with the same genetic disorder. Litchfield *et al.* (19) found, in an overview of 27 pedigrees with a total of 167 GRA+ affected members, a prevalence of 72.7% of hypertension. The average age of onset of hypertension was 17.8 yr. Furthermore, 18% of the GRA+ patients had a stroke; and in these patients, the average age of onset of hypertension was 12.3 yr. In Australian patients, the prevalence of hypertension was reported as 59% in GRA+ subjects and 33% in patients aged less than 20 yr (27). In other reports of single pedigrees, the prevalence of hypertension was 100% before reaching 27 yr of age (28, 29). The family reported in this work displays a mild phenotype, with an average BP level for the GRA+ patients of 131/86 mm Hg and no subjects with hypokalemia.

TABLE 3. Linear regression analysis (stepwise)

SBP	Variable	$\beta \pm$ SEM	Partial R^2	Total R^2	P
	Intercept	110.1 ± 18.9			<0.0001
	Age	1.25 ± 0.2	0.48	0.48	<0.0001
	18OHF	0.13 ± 0.008	0.14	0.62	0.001
	Sex	−11.2 ± 6.27	0.03	0.65	0.11
	BMI	−1.61 ± 1.04	0.02	0.67	0.13
	PAL	[a]			
	18oxoF	[a]			
	Kallikrein	[a]			
DBP	Intercept	49.0 ± 4.9			<0.0001
	Age	0.57 ± 0.11	0.38	0.38	<0.0001
	18OHF	0.02 ± 0.006	0.18	0.56	0.0006
	Sex	[a]			
	BMI	[a]			
	PAL	[a]			
	18oxoF	[a]			
	Kallikrein	[a]			

The analysis was performed using SBP and DBP as dependent variables and using age, BMI, sex (male = 0 female = 1), PAL, 18OHF, and 18oxoF as independent variables. R^2 is the proportion of the variance that is predictable from the regressor variables.

[a] These variables did not enter into the model.

Further, no patient developed hypertension before the age of 18 yr, and only 3 before the age of 36 yr. Also, the occurrence of stroke was very low and could even be unrelated to the GRA+ genotype, because the only patient with this complication in our family was normotensive until the age of the event, and all the reported patients having stroke were hypertensive at the time (19). A previous study reported a 6% prevalence of PE in GRA+ women, 39% of PAH, and 32% of cesarean section (20). In our family, we didn't observe any case of PE or PAH, and no cesarean sections were performed. Finally, the newborns with GRA+ mothers had normal birth weights and didn't show any complications after the birth.

To investigate the basis of these clinical findings, we evaluated the biochemical parameters of this family. Upright PAL was not significantly different between GRA+ and GRA−, in agreement with a previous report (22). Hybrid steroid levels (and, in particular, urinary 18OHF levels) are the best biochemical indicators of GRA status. In our study, we found a strong correlation among PAL, urinary 18OHF, and 18oxoF, indicating that all are dependent on the unregulated hyperactivity of the hybrid enzyme. However, in our multiple regression analysis, only 18OHF was a strong predictor of the BP levels; in particular, in our model, 18OHF accounted for 14% and 18% of the variance of the SBP and DBP, respectively. Others have found a correlation between aldosterone and 18oxoF and BP levels, but 18OHF was not evaluated (22). It is supposed that 18OHF has a weak effect on sodium reabsorption; we suggest that the observed correlation with BP levels is more likely attributable to the fact that 18OHF could be the best indicator of the hybrid gene activity. In this family, the 18OHF displays the same sensitivity and specificity of the genetic test in identifying GRA+ patients. Mosso *et al.* (30) recently reported similar findings with the serum 18OHF assay. 18oxoF displayed the same sensitivity; but in 1 case, a GRA−patient had high levels of this hormone. Furthermore, some of the GRA+ patients had 18oxoF levels that were not clearly higher than the normal range. Taken together, these data show a relevant role of 18OHF on BP levels. Only 18OHF and age were independent predictors of BP levels; BMI and sex were entered into the regression model but had a small (2% and 3% of SBP variance, respectively) and not significant effect on these clinical parameters of our population. Aldosterone levels, kallikrein, and 18oxoF did not enter into the model; 18OHF and age were the strongest predictors of BP levels, accounting for 62% and 56% of variance of the SBP and the DBP, respectively.

In conclusion, we have described a large pedigree in which a GRA+ status has been demonstrated throughout four generations. The phenotype of this family is particularly mild when compared with families described previously. None of the biochemical or genetic characteristics explain this mild phenotype; furthermore, there is no data about possible protection against hypertension and its consequences in Sardinians. We suggest that other genetic and environmental interactions determine the low morbidity and mortality in this GRA family.

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