Adrenal crisis and \( BclI \) polymorphism of the glucocorticoid receptor and adrenal crisis in primary adrenal insufficiency

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Abstract

**Context**: Patients with primary adrenal insufficiency (PAI) or congenital adrenal hyperplasia (CAH) are at a high risk of adrenal crisis (AC). Glucocorticoid sensitivity is at least partially genetically determined by polymorphisms of the glucocorticoid receptor (GR).

**Objectives**: To determine if a number of intercurrent illnesses and AC are associated with the GR gene polymorphism \( BclI \) in patients with PAI and CAH.

**Design and patients**: This prospective, longitudinal study over 37.7 ± 10.1 months included 47 PAI and 25 CAH patients. During the study period, intercurrent illness episodes and AC were documented.

**Results**: The study period covered 223 patient years in which 21 AC occurred (9.4 AC/100 pat years). There were no significant differences between \( BclI \) polymorphisms (CC (\( n = 29 \)), CG (\( n = 34 \)) and GG (\( n = 9 \)) regarding BMI, hydrocortisone equivalent daily dose and blood pressure. We did not find a difference in the number of intercurrent illnesses/patient year among \( BclI \) polymorphisms (CC (1.5 ± 1.4/pat year), CG (1.2 ± 1.2/pat year) and GG (1.6 ± 2.2/pat year)). The occurrence of AC was not significantly different among the homozygous (GG) genotype (32.5 AC/100 pat years), the CC genotype (6.7 AC/100 pat years) and the CG genotype (4.9 AC/100 pat years). Concomitant hypothyroidism was the highest in the GG genotype group (5/9), compared to others (CC (11/29) and CG (11/34)).

**Conclusions**: Although sample sizes were relatively small and results should be interpreted with caution, this study suggests that the GR gene polymorphism \( BclI \) may not be associated with the frequencies of intercurrent illnesses and AC.

Introduction

Polymorphisms of the glucocorticoid receptor (GR) may influence the sensitivity to glucocorticoids by altering the GR expression (e.g. reducing transcription) and influencing transactivation and transrepression of target genes. The \( BclI \) single nucleotide polymorphism (SNP) (C>G) is known to increase glucocorticoid sensitivity (1, 2, 3). This GR polymorphism works as part of a conserved haplotype and has repeatedly been associated with mood disorders and psychopathology (4), such as hypomania (5) and bulimia nervosa (6). The \( BclI \) polymorphism has...
also been associated with hypertension (7), metabolic syndrome (8), and especially hyperinsulinemia and obesity (9) indicating that the BclI SNP may alter GR functionality. In patients with bronchial asthma, the BclI polymorphism seems to at least partially explain the development of a severe form of asthma associated with resistance to glucocorticoids (10).

Patients with adrenal insufficiency need a lifelong glucocorticoid replacement therapy (11, 12), which needs to be tailored individually to the daily needs, to stress situations, and intercurrent illnesses such as infectious diseases (13). This is even more important since the daily dose of hydrocortisone was lowered in recent years to an average of 20mg per day. Failure of dose adaptations in situations with a high need for glucocorticoids is likely to lead to adrenal crisis (AC), which is a major threat to patients with AI (14) and a major cause for the increased mortality (15). The pathogenesis and progression of AC are still not well understood, but glucocorticoid resistance due to increased tumor necrosis factor α (TNF-α) seems to play a major role (16, 17, 18, 19).

Recently, we could show that bone mineral density in patients with adrenal insufficiency is at least partially dependent on the BclI polymorphism of the GR (20). This triggers the question if intercurrent illnesses, their duration and the occurrence of AC might be influenced by the BclI polymorphism. Therefore, we included 72 patients with adrenal insufficiency (47 patients with primary adrenal insufficiency (PAI) and 25 patients with congenital adrenal hyperplasia (CAH)) in a prospective documentation of their intercurrent illness episodes and their AC frequency over a mean of 37.7 months. In all patients, the BclI polymorphism was determined and the groups with wild-type (CC), homozygous mutant (GG) and heterozygous mutant (CG) genotypes were compared regarding intercurrent illnesses and AC.

### Methods

#### Design and patients

In a prospective study, patients from one endocrine university outpatient clinic were included. Inclusion criteria were PAI or CAH verified by reviewing medical records. Patients under the age of 18 years, patients diagnosed with bone metastasis, secondary adrenal insufficiency, adrenal insufficiency due to long-term pharmacological glucocorticoid treatment, adrenocortical carcinoma and patients with less than 12 months duration of disease were excluded. The study protocol was approved by the Charite University hospital ethics committee (EA1/027/10) and all patients gave written informed consent prior to participation. All clinical data, including the nature of hormone replacement therapies, were documented. The dose of glucocorticoid was converted into milligrams of hydrocortisone equivalent (0.29 mg dexamethasone = 3.33 mg prednisolone = 20 mg hydrocortisone) (21). The daily hydrocortisone equivalent intake was corrected for body surface area.

Forty-seven patients suffering from PAI (36 women, 11 men) and 25 patients with CAH (14 women, 11 men; salt-wasting n=17, simple-virilizing n=8) were included in the study. Most patients with PAI were treated with hydrocortisone (n=35) or prednisolone (n=11). Patients with CAH were treated with either hydrocortisone (n=10), prednisolone (n=5) or dexamethasone (n=3) alone, or a combination of prednisolone and/or dexamethasone (n=1), a combination of hydrocortisone and dexamethasone (n=4) or a combination of hydrocortisone and prednisolone (n=2). Cohort characteristics are displayed in Table 1.

#### Clinical follow-up

During the study period, patients attended the endocrine outpatient clinic on a regular basis (on average, every six months). All patients were instructed on glucocorticoid dose adaptation: Doubling the replacement dose in the case of minor stress like flu-like symptoms, tripling or quadrupling the dose in the case of high fever or severe infections, intravenous hydrocortisone administration in the case of major stress like surgery, trauma or delivery. Patients were further instructed to immediately contact emergency care for parenteral hydrocortisone administration in the case of vomiting and diarrhea and received information on how to perform self-treatment in the case of unavailability of health care professionals (glucocorticoid self-injection, use of glucocorticoid suppositories). Patients were instructed to record information on days with intercurrent illnesses or an AC (parenteral glucocorticoid administration) in a patient’s diary. This diary was checked throughout the study period, collected at the study end and the number of days with intercurrent illnesses and the events with parental glucocorticoid administration extracted. AC was defined if the following condition could be documented: Worsening of the general condition with signs and symptoms of glucocorticoid deficiency and at least two of...
the following findings demanding subsequent parenteral glucocorticoid administration: hypotension (systolic blood pressure <100 mmHg), nausea or vomiting, severe fatigue, hyponatremia, hyperkalemia or hypoglycemia (17). Situations with parenteral glucocorticoid administration were evaluated retrospectively by the treating endocrinologists if they fulfilled the criteria of an AC crosschecking on the information from the patient (symptoms and complaints), from the protocol of the emergency services and from the reports of the hospital. Intercurrent illness was defined as any temporal illness where a transient increase in the glucocorticoid replacement dose was needed. The duration of the intercurrent illness was given by the number of days with complaints due to this event documented by the patient in the diary.

Analysis of GR gene polymorphism BclI

The recently described PCR method detects not only homozygous wild-type (CC) and homozygous mutant (GG), but also heterozygous mutant (CG) genotypes: in addition to a 418-bp fragment present in all samples, homozygous wild-type individuals produce a 177-bp fragment, whereas homozygous mutant subjects have a 284-bp fragment (22). Total genomic DNA was isolated and PCR performed as reported previously (20). The following oligonucleotide primers were used: a reverse primer specific for the wild-type allele (5-CAATTCCTCTCTTAAAGAGATTG-3), a forward primer specific for the mutant allele (5-GACAA-GTTATGCTTGCTGATG-3) and an outer forward (5-AGAGCCCTATTCTTCAAACTG-3) and reverse primer (5-GAGAAATTTACCCTACCAAC-3) (Eurofins MWG Operon, Ebersberg, Germany).

Statistical analysis

For a better clinical understanding, we calculated and displayed the frequency of AC as the number of AC per 100 patient years, whereas we calculated the frequency of intercurrent illnesses as the number of intercurrent illnesses per patient year.

Associations between genotypes and clinical features were evaluated using one-way ANOVA and Kruskal–Wallis ANOVA depending on normality distribution. Post hoc pairwise comparison between groups was tested for significance using the Bonferroni test to correct for multiple comparisons. The statistical analysis of frequencies was performed by Chi-Square Test and Fisher’s Exact test.

Analyses were performed using the statistical software package SPSS, version 15.0 (SPSS). Significance was accepted if $P < 0.05$.

Results

The study period covered 223 patient years in which 21 AC occurred (9.4 AC/100 pat years) showing a trend of more frequent ACs in PAI than in CAH patients (9.99 vs 8.08 AC/100 pat years) (Table 2). However, the percentage of patients with an AC during the study period was not different

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Table 1  Clinical data of patients with primary adrenal insufficiency (PAI) and congenital adrenal hyperplasia (CAH) included in the study.

|                      | All (n=72) | Primary adrenal insufficiency (n=47) | Congenital adrenal hyperplasia (n=25) |
|----------------------|------------|--------------------------------------|--------------------------------------|
| Male/female          | 22/50      | 11/36                                | 11/14                                |
| Age (years)          | 50.4 ± 16.3 | 56.3 ± 15.3                          | 39.2 ± 12***                         |
| BMI (kg/m²)          | 26.4 ± 5.9  | 25.6 ± 4.6                           | 27.8 ± 7.6                          |
| Duration of disease (years) | 25.2 ± 13.6 | 19.9 ± 11.8                          | 35.0 ± 11.3***                      |
| Daily HC-equivalent dose (mg) | 26.5 ± 9.7  | 25.8 ± 8.6                           | 28.0 ± 11.5                         |
| GC-dose per body surface (mg/m²) | 14.8 ± 5.8  | 14.4 ± 5.9                           | 15.6 ± 5.9                          |
| Fludrocortisone daily dose (mg) | 0.11 ± 0.08 (n=61) | 0.10 ± 0.07 (n=44) | 0.14 ± 0.09 (n=17) |
| DHEA daily dose (mg) | 20.8 ± 6.6 (n=15) | 20.8 ± 6.6 (n=15) | – (n=0) |
| Concomitant disease  |             |                                      |                                      |
| Hypothyroidism       | 27/72      | 23/47                                | 4/25                                 |
| Diabetes mellitus    | 13/72      | 12/47                                | 1/25                                 |
| Primary ovarian failure | 4/50       | 3/36                                 | 1/14                                 |
| Asthma               | 5/72       | 1/47                                 | 4/25                                 |

Data are means ± s.d.

***P < 0.001 compared to PAI.

BMI, body mass index; DHEA, dehydroepiandrosterone; GC, glucocorticoid; HC, hydrocortisone.
### Table 2  Clinical data, intercurrent illnesses and adrenal crisis (AC) during the study period in patients with primary adrenal insufficiency (PAI) or congenital adrenal hyperplasia (CAH).

|                        | Study start |                                                      | Study end |                                                      |
|------------------------|-------------|-------------------------------------------------------|-----------|-------------------------------------------------------|
|                        | All (n = 72)| Primary adrenal insufficiency (n = 47) | Congenital adrenal hyperplasia (n = 25) | All (n = 72)| Primary adrenal insufficiency (n = 47) | Congenital adrenal hyperplasia (n = 25) |
| BMI (kg/m²)            | 26.4 ± 5.9  | 25.6 ± 4.6                                          | 27.8 ± 4.2| 26.3 ± 4.8                                           | 25.8 ± 4.8                                          | 27.4 ± 4.6 |
| Daily HC-equivalent dose (mg) | 26.5 ± 9.7  | 25.8 ± 8.6                                          | 28.0 ± 11.5| 25.4 ± 7.1                                           | 25.0 ± 7.1                                          | 26.2 ± 7.3 |
| HC-equivalent dose per body surface (mg/m²) | 14.8 ± 5.8  | 14.4 ± 5.9                                          | 15.6 ± 5.9| 14.1 ± 4.4                                           | 13.9 ± 4.9                                          | 14.5 ± 3.2 |
| Fludrocortisone (mg/day) | 0.11 ±0.08 (n=61) | 0.10 ±0.07 (n=44)                                  | 0.14 ±0.09 (n=17) | 0.11 ±0.09 (n=61)                                   | 0.11 ±0.06 (n=44)                                   | 0.12 ±0.08 (n=17) |
| Blood pressure (mmHg)  | 119 ± 16/75 ± 8 | 119 ± 16/74 ± 8                                     | 120 ± 15/76 ± 8 | 126 ± 16/79 ± 8                                      | 126 ± 17/78 ± 8                                     | 126 ± 16/81 ± 7 |
| Intercurrent illnesses per patient year | –          | –                                                   | –                                                   | 1.38 ± 1.42                                         | 1.57 ± 1.57                                         | 0.99 ± 0.98 |
| % of days with intercurrent illness | –          | –                                                   | –                                                   | 2.49 ± 2.96                                         | 2.59 ± 2.68                                         | 2.28 ± 3.50 |
| No. of pat with AC     | –          | –                                                   | –                                                   | 10                                                  | 6                                                   | 4       |
| No. of AC during study period | –          | –                                                   | –                                                   | 21                                                  | 15                                                  | 6       |
| AC per 100 patient years | –          | –                                                   | –                                                   | 9.41                                                | 9.99                                                | 8.08    |

Means ± s.d.
BMI, body mass index; HC, hydrocortisone.
between PAI and CAH. 9 ACs were rated grade 1 and 12 ACs were rated grade 2 (grading according to Allolio (17)).

During the study period, BMI, daily HC-equivalent dose, fludrocortisone dose and blood pressure did not show any significant change (Table 2).

During the study period, a total of 310 episodes of intercurrent illness occurred. All episodes summarized up to a total of 1933 days with a mean duration of 6.2 days of an intercurrent illness episode. Patients experienced 1.38 intercurrent illnesses per patient year (2.49% of all days were the days with intercurrent illnesses) without any significant differences between PAI and CAH patients (Table 2).

There were no significant differences among the three BclI polymorphisms (CC (n=29), CG (n=34) and GG (n=9)) regarding BMI, hydrocortisone equivalent daily dose and blood pressure (Table 3).

We did not find a difference in the number of intercurrent illnesses/patient year among the three BclI polymorphisms (CC (1.5±1.4/pat year), CG (1.2±1.2/pat year) and GG (1.6±2.2/pat year)). The occurrence of AC was not significantly different among the homozygous (GG) genotype (32.5 AC/100 pat years), the CC genotype (6.7 AC/100 pat years) and the CG genotype (4.9 AC/100 pat years) (Table 3). However, this tendency to higher frequency of AC in the homozygous (GG) genotype group was mainly due to one patient who had 8 ACs in the study period.

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Concomitant hypothyroidism was the highest in the GG genotype group (5/9), compared to other groups (CC (11/29) and CG (11/34)), whereas diabetes mellitus was most common in the CG genotype group.

### Discussion

ACs occur in a substantial proportion of patients with adrenal insufficiency with an overall frequency of 5–17 AC/100 patient years in retrospective studies (23, 24, 25, 26, 27), and 8.3 AC/100 patient years in a prospective study (14). Our current study shows a frequency of 10 AC/100 patient years in PAI and 8.1 AC/100 patient years in adult CAH patients. The latter is quite higher than the recently reported data (4.8–5.8 AC/100 pat years) from a retrospective CAH cohort (28). This might be due to the relatively high proportion of salt-wasting CAH patients in our cohort. Interestingly, all ACs occurred in the group of CAH patients with the salt-wasting form, leading to a frequency of 11.5 AC/110 patient years in this group.

Precipitating causes of AC are mainly gastrointestinal infection, fever and other infections. Patients with additional comorbidities, such as diabetes mellitus, asthma, premature ovarian failure or hypothyroidism, are at a higher risk (14, 23, 24).

The pathogenesis and progression of AC are still not well understood. It is suspected that TNF-α plays a major role in the pathogenesis of AC. TNF-α is required for the expression of adrenal glucocorticoid receptors, which in turn leads to increased glucocorticoid sensitivity and the development of AC (29). The GG genotype is known to have increased glucocorticoid sensitivity compared to the CG and CC genotypes. Means ± s.d.

### Table 2

| BclI allelic variants | CC | CG | GG |
|-----------------------|----|----|----|
| N (female/male)       | 29 (20/9) | 34 (23/11) | 9 (7/2) |
| PAI/CAH               | 19/10 | 22/12 | 6/3 |
| Age (years)           | 48.3±15.8 | 50.3±14.2 | 57.6±24.2 |
| BMI (kg/m²)           | 26.6±7.2 | 25.7±4.2 | 27.4±6.7 |
| Duration of disease (years) | 25.4±14.5 | 26.6±12.9 | 19.1±12.8 |
| Daily HC-equivalent dose (mg) | 26.1±8.9 | 27.2±11.3 | 25.5±4.9 |
| HC-equivalent dose per body surface (mg/m²) | 14.4±4.7 | 15.4±7.2 | 14.1±2.9 |
| Blood pressure (mmHg) | 117±13/73±8 | 120±16/76±8 | 124±22/76±7 |
| Fludrocortisone (mg/day) | 0.08±0.05 | 0.11±0.10 | 0.07±0.02 |
| Concomitant disease (n) | | | |
| Hypothyroidism        | 11 | 11 | 5 |
| Diabetes mellitus     | 4 | 8 | 1 |
| Primary ovarian failure | 4 of 20 | 0 | 0 |
| Asthma                | 0 | 4 | 1 |
| Intercurrent illnesses per patient year | 1.50±1.43 | 1.22±1.15 | 1.58±2.24 |
| % of days with intercurrent illness | 2.0±1.8 | 2.7±3.3 | 3.2±4.4 |
| No. of pat with AC    | 4 | 3 | 3 |
| No. of AC during study period | 6 | 5 | 10 |
| AC per 100 patient years | 6.67 | 4.89 | 32.47 |

The GG genotype is known to have increased glucocorticoid sensitivity compared to the CG and CC genotypes. Means ± s.d.
role. TNF-α levels increased considerably after endotoxin administration in adrenalectomized mice (19) and induced glucocorticoid insensitivity (20). A mice model with adrenal insufficiency showed an aberrant inflammatory response in sepsis (16). It is suspected that glucocorticoid resistance due to increased TNF-α might also play a major role in the pathophysiology of AC in humans (17).

As GR resistance plays a role in AC, we wanted to investigate the hypothesis if AI patients who carry a polymorphism of the GR leading to a more insensitive GR receptor are more prone to end up in an AC.

In our cohort, the more sensitive GG nucleotide of the BclI polymorphism was associated with a tendency to lower daily HC-equivalent doses and to higher BMI. In addition, there was also a tendency to more days with intercurrent illnesses in this group compared to the CC and CG nucleotides. However, this tendency might be explained by the higher frequency of hypothyroidism in this group. The latter is considered to be a risk factor for AC (23). We could not identify a significant difference between the nucleotide types of the BclI polymorphism regarding AC.

These are the first data regarding the number of intercurrent illnesses and the percentage of days with intercurrent illnesses with regard to the BclI polymorphism of the GR. It is interesting to note that a patient with AI had on average 9 days with intercurrent illnesses per year. This is comparable to the average number of sick days of German employees (10.8 days in 2016) (30). In addition, the average duration of an intercurrent illness was 6.5 days in patients with AI.

There are several limitations in this study. First, we used a relatively small patient cohort for a genetic association study and therefore the results need further replication. However, the strength of our study is the long study period with an average of 37.7 months. Second, it is still unknown how the BclI polymorphism exerts its effects. After administration of dexamethasone, serum cortisol levels were lower in G-allele carriers of the BclI polymorphism, explaining by the higher frequency of hypothyroidism in this group. The latter is considered to be a risk factor for AC (23). We could not identify a significant difference between the nucleotide types of the BclI polymorphism regarding AC.

In conclusion, we could neither detect a significant difference in the frequency and duration of intercurrent illness episodes nor in the frequency of AC regarding the BclI polymorphism of the GR.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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