Surviving ectopic Cushing's syndrome: quality of life, cardiovascular and metabolic outcomes in comparison to Cushing's disease during long-term follow-up

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Abstract

Objective: Aim of our study was to analyze long-term outcome of patients with the ectopic Cushing's syndrome (ECS) compared to patients with Cushing's disease (CD) regarding cardiovascular, metabolic, musculoskeletal and psychiatric comorbidities.

Design: Cross-sectional study in patients with ECS and CD in two German academic tertiary care centers.

Methods: Standardized clinical follow-up examination was performed including health-related quality of life (QoL) in 21 ECS patients in long-term remission (≥ 18 months since successful surgery). Fifty-nine patients with CD in remission served as controls.

Results: Time from first symptoms to diagnosis of Cushing's syndrome (CS) was shorter in ECS than in CD (8.5 (IQR: 30.3) vs 25 (IQR: 39.0) months, $P=0.050$). ECS patients had lower self-reported psychiatric morbidity compared to CD (19% vs 43%, $P=0.050$) at follow-up. Moreover, female ECS patients reported favorable scores for QoL in the SF-36 questionnaire (mental health: 92 (IQR: 30) vs 64 (IQR: 32) in CD, $P=0.010$) and a Cushing-specific QoL questionnaire (73 (IQR: 18) vs 59 (IQR: 36) in CD, $P=0.030$). In a pooled analysis of ECS and CD patients, QoL correlated with time from first symptoms until diagnosis of CS, but not with urinary free cortisol levels or serum cortisol after dexamethasone at the time of diagnosis. Long-term outcomes regarding hypertension, metabolic parameters, bone mineral density and grip strength were comparable in ECS and CD.

Conclusions: Our data support the concept that time of exposure to glucocorticoid excess appears to be a better predictor than peak serum cortisol levels at the time of diagnosis regarding long-term psychiatric morbidity and QoL.

European Journal of
Endocrinology
(2018) **179**, 109–116

Introduction

Endogenous Cushing's syndrome (CS) is a disabling disease caused by autonomous glucocorticoid production (1). Overall, 80% of the cases are ACTH dependent, predominantly by ACTH-secreting pituitary adenomas

(Cushing's disease, CD) (2). In approximately 20% of ACTH-dependent CS, ACTH is produced by non-pituitary neuroendocrine tumors causing the ectopic Cushing's syndrome (ECS) (3). ECS is associated with a large variety of

benign and malignant tumors. The most frequent origins are small-cell lung carcinomas (SCLC), lung carcinoids or neuroendocrine tumors (NETs) of the entero-pancreatic system, pheochromocytomas and medullary thyroid carcinomas (4, 5, 6). Cases with unknown source of ACTH production have been designated as occult ectopic CS (7).

The clinical presentation and prognosis of ECS depends widely on the malignant potential of the underlying tumor. Moreover, CS itself is associated with enhanced cardiovascular risk, psychiatric comorbidities, musculoskeletal impairment, osteoporosis and decreased quality of life (QoL) (8, 9, 10, 11, 12, 13).

The therapy of choice for ECS depends on tumor identification, localization, staging and classification (14). The most effective treatment is the removal of the ACTH producing tumor (7). If this is not possible, medical therapy, radiotherapy and bilateral adrenalectomy (BADx) are further options to control cortisol excess (14).

To date, the outcome of ECS patients has been reported as part of retrospective studies only. Therefore, our goal was to analyze the long-term outcome of all our ECS patients regarding biochemical and clinical outcomes as well as morbidity and mortality in a prospective cross-sectional study.

Subjects and methods

Patient cohort

Patients with ECS were recruited in two German academic tertiary care centers (Medizinische Klinik IV, Munich ($n=30$); Division of Endocrinology and Diabetes, Department of Internal Medicine I and University Hospital Würzburg ($n=26$). Patients with CD treated in Munich ($n=59$) were used as a comparative cohort. The analysis was restricted to patients treated since 1990. Epidemiologic, clinical and biochemical data were extracted from patient's files and entered into an electronic data base. All surviving patients with a follow-up time after remission of at least 18 months were contacted and asked to participate in a long-term evaluation within the German's Cushing's Registry CUSTODES (15).

Information on medical history and socio-demographic characteristics were obtained by trained and certified staff members during a personal interview. Moreover, the participants underwent a standardized medical examination, including blood sampling, evaluation of waist-to-hip ratio and measurements of muscle strength and blood pressure. The latter was measured three times on both arms in seated position

after 5 min of rest. The mean of the three measurements was used for statistical analysis. Grip strength was assessed with the Jamar hydraulic hand dynamometer (Sammons Preston, Rolyan). Mean values of three trials of the leading hand were calculated and compared to mean values of an age- and gender-matched normative population (16). The chair rising test measured the time for rising from a chair (height of 45 cm) five times at maximum speed. The patient started while seated and ended while standing. Blood samples were taken in the morning from fasting, seated subjects.

The study was approved by the local ethical committees (Ethikkommission bei der Medizinischen Fakultät der LMU München and Ethikkommission bei der Medizinischen Fakultät der Universität Würzburg) and all patients provided written informed consent.

Biochemical measurements

Twenty-four-hour urinary free cortisol was measured with the Liaison Assay (DiaSorin) or with RIA (Immunotech-Assay, Beckman-Coulter). ACTH and serum cortisol were measured with the Liaison Assay (DiaSorin) or with Immulite (Siemens Healthineers). All other biochemical variables were assayed in the central laboratories of the two participating centers, using standardized analytical methods.

Definitions

Subjects with blood pressure $\geq 140/90$ mmHg, self-reported history of hypertension or intake of antihypertensive medication were classified as hypertensive. Diabetes was defined by HbA1c $\geq 6.5\%$ or intake of antidiabetic drugs. Osteoporosis was defined by T -values ≤ -2.5 s.d. using dual energy X-ray absorptiometry. Cushing's stigmata included a large variety of symptoms regarded as disease specific (e.g. moon face, buffalo hump, hirsutism or skin alterations). Muscle weakness was defined by the self-reported disability to rise from knee bending without the aid of arms. Psychiatric morbidities included self-reported anxiety, depression, panic attacks or psychosis. Remission from CS was defined by normalization of dexamethasone suppressed serum cortisol ($<1.8 \mu\text{g/dL}$) or dependence on glucocorticoid substitution.

QoL questionnaires

A generic health-related QoL questionnaire (SF-36 Health Survey) (17) and two disease-specific instruments

(Tuebingen CD-25 (18) and Cushing QoL (13)) were used for the assessment of QoL. In each of these questionnaires, values can range from 0 to 100. In the SF-36 Health Survey and in Cushing QoL higher scores indicate better QoL, whereas in Tuebingen CD-25 lower scores indicate better QoL.

Statistical analysis

Data were extracted from the German Cushing's Registry CUSTODES. If not stated otherwise, results are expressed as median and interquartile range (IQR). Data between groups were compared using χ^2 -test (2-sided), Mann-Whitney *U* test or Kruskal-Wallis test. Survival was analyzed using Kaplan-Meier curves. Concerning health-related QoL, Mann-Whitney *U* test was used for comparison of scores between different patient groups. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using standard statistical software (SPSS 21, IBM).

Results

Description of the entire study cohort

In total, 56 patients with ECS treated since 1990 were identified. Causes of ECS, among others, were lung

carcinoids ($n = 19$; 34%), small-cell lung carcinoma ($n = 6$; 11%), pancreatic NETs ($n = 3$; 5%) and occult ECS ($n = 15$; 27%). The cause of ECS was not found in any of the occult cases even though functional imaging was performed during follow-up in some cases. As provided in Table 1, clinical and biochemical data at initial diagnosis did not significantly differ according to cause of ECS, except for ACTH values (highest value in occult ECS, $P = 0.019$).

The majority of ECS patients were females (59%). Median age at diagnosis was 57 years (IQR: 24) and median time until diagnosis was 6 months (IQR: 18).

Twenty-nine (52%) of the 56 patients received oncologic resection of the ectopic ACTH source and 24 (43%) underwent BADx during the course of treatment either as first line therapy ($n = 10$) or following unsuccessful endocrine control ($n = 14$). Eight of 56 patients (14%) had a retrospectively unjustified transsphenoidal surgery, mostly because bilateral inferior petrosal sinus sampling (IPSS) was not performed before transsphenoidal surgery. Only in one case IPSS falsely indicated a pituitary ACTH secretion.

Survival was significantly different in patients with different causes of ECS (Fig. 1, $P = 0.000$). Median survival rates were 5 (IQR: 7) months in patients with SCLC (5 of 6 patients deceased at last follow-up), 53 (IQR: 97) months in patients with an occult source of ECS (4 of 15 patients deceased) and 119 (IQR: 149) months in patients

Table 1 Clinical and biochemical parameters at initial diagnosis of ectopic Cushing's syndrome (ECS) according to the underlying disease. Results are presented as median (IQR), *n*.

	Lung carcinoid	Occult	SCLC	Others
<i>n</i>	19	15	6	16
Females/males	11/8	11/4	2/4	9/7
Age at diagnosis in years	51 (30), 19	67 (21), 15	64 (18), 6	55 (22), 16
Time from first symptoms to diagnosis in month	18 (29), 18	4 (22), 14	5 (8), 5	2 (13), 13
Clinical evaluation				
Systolic blood pressure (mmHg)	150 (35), 15	144 (38), 12	122 (44), 6	142 (23), 7
Diastolic blood pressure (mmHg)	91 (10), 15	85 (23), 12	87 (27), 6	90 (12), 7
BMI (kg/m ²)	28 (10), 18	27 (10), 14	28 (3), 6	25 (7), 8
Cushing stigmata	94%, 18	100%, 14	80%, 5	82%, 11
Psychiatric morbidity	38%, 16	27%, 11	33%, 3	29%, 7
Biochemistry				
HbA1c (%)	6.0 (1.8), 12	5.9 (1.3), 11	7.0 (0.0), 3	7.0 (1.1), 6
ACTH (pg/mL)	91 (65), 19	157 (189), 14	125 (904), 6	66 (291), 13
UFC (μg/24 h)	944 (1536), 17	1531 (1882), 11	1150 (2391), 4	959 (4906), 9
DXM (μg/dL)	27 (13), 15	56 (21), 12	31 (102), 5	24 (75), 12
Midnight salivary cortisol (μg/L)	24 (41), 7	70 (76), 7	22 (0), 3	45 (5627), 4

Conversion from ACTH in pg/mL to SI units (pmol/L) is performed by multiplication by 0.22.

BMI, body mass index; DXM, serum cortisol after 1mg dexamethasone; SCLC, small cell lung carcinoma; UFC, urinary free cortisol.

Overall survival

Figure 1

Kaplan–Meier analysis on overall survival for ectopic Cushing's syndrome entities. Lung carcinoids $n=16$, occult $n=13$, SCLC $n=6$, others $n=14$.

with lung carcinoids. In the latter group, 2 of 19 patients deceased within 4 and 7 months.

Standardized follow-up investigation

Six of 56 retrospectively identified patients with ECS were lost to follow-up. Of the remaining 50 patients, 22 (44%) had died, 5 (10%) refused to undergo a standardized follow-up examination and 2 (4%) had a time since remission of <18 months. The other 21 patients (13 lung carcinoids, 5 occult tumors, 3 other tumors) underwent standardized follow-up examination.

The data were compared to that of 59 patients with CD in remission studied similarly. The examinations took place after a median remission time of 73 (IQR: 92) months in ECS and 105 (IQR: 182) months in CD.

Clinical and biochemical parameters during follow-up

The 21 ECS patients with standardized follow-up were either treated by surgery of the ectopic tumor ($n=11$) or by BADx ($n=10$). ECS and CD patients in remission did not differ significantly regarding cardiovascular comorbidities (Table 2) or clinical and biochemical characteristics (Table 3).

Table 2 Clinical appearance and relevant comorbidities in patients with ectopic Cushing's syndrome (ECS) and Cushing's disease (CD) in long-term remission.

	ECS (n (%))	CD (n (%))	P
High blood pressure	16/21 (76)	33/59 (56)	ns
Diabetes mellitus	3/21 (14)	9/59 (15)	ns
Dyslipidemia	12/20 (60)	46/59 (78)	ns
Osteoporosis	3/13 (23)	4/44 (9)	ns
Cushing's stigmata	2/21 (10)	10/59 (17)	ns
Muscle weakness	5/21 (24)	7/59 (12)	ns
Psychiatric morbidity	4/21 (19)	25/58 (43)	0.050

QoL assessment during follow-up

Self-reported psychiatric morbidity was not different between ECS and CD during the active phase of their disease (ECS: 37% vs CD: 52%, $P=ns$). During follow-up, however, a significantly lower frequency was observed in the ECS group (ECS: 19% vs CD: 43%, $P=0.050$). Moreover, female ECS patients reported better health-related QoL compared to female CD patients at follow-up (Table 4). In detail, this subgroup showed significantly higher scores regarding vitality (ECS 60 vs CD 40, $P=0.033$), emotional role (100 vs 67, $P=0.043$) and mental health (92 vs 64, $P=0.010$) in the health-related SF-36 questionnaire. Female ECS patients also had favorable scores in the Cushing-specific questionnaires Cushing QoL (ECS 73 vs CD 59, $P=0.030$) and Tuebingen CD-25 (ECS 17 vs CD 25, $P=ns$), implicating a better QoL. Male ECS and CD patients showed no significant difference in health-related and disease-specific QoL. QoL correlated with time from first symptoms until diagnosis (SF-36 physical functioning ($r=-0.33$; $P=0.010$; $n=61$), bodily pain ($r=-0.39$; $P=0.002$; $n=61$), general health ($r=-0.29$; $P=0.024$; $n=61$), vitality ($r=-0.29$; $P=0.02$; $n=61$) and social functioning ($r=-0.26$; $P=0.043$; $n=61$)), but not with urinary free cortisol (UFC) levels or serum cortisol after dexamethasone at diagnosis in a pooled analysis of ECS and CD patients. No ECS patient had evidence for pituitary insufficiency. In contrast, 35% and 36% of female and male patients with CD, respectively, had pituitary insufficiency, mostly complete or incomplete anterior pituitary insufficiency and received replacement therapy as required. 22% of the CD patients underwent radiotherapy. At the time of the follow-up examination, the prevalence of females (45 vs 65%, $P=ns$) and males (57 vs 73%, $P=ns$) on hydrocortisone substitution was comparable between ECS and CD patients. There was no significant impact of the presence of pituitary insufficiency, radiotherapy or

Clinical Study	A Osswald, T Deutschbein and others	Surviving ectopic Cushing's syndrome	179:2	113
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Table 3 Clinical and biochemical outcome in patients with ectopic Cushing's syndrome (ECS) and Cushing's disease (CD) in long-term remission. Data are presented as median (IQR), *n*.

	ECS (<i>n</i> =21)	CD (<i>n</i> =59)	
Females/males	14/7	45/14	ns
Age at last follow-up in years	65.0 (21.0), 21	50.6 (17.0), 59	ns
Time from first symptoms to diagnosis in months	8.5 (30.3), 20	25.0 (39.0), 51	0.050
Time from diagnosis until remission in months	1.0 (28.0), 21	3.0 (37.0), 59	ns
Time from first symptoms until remission in months	24.5 (109.3), 20	43.0 (71.0), 51	ns
Follow-up time since remission in months	73.0 (92.0), 21	105.0 (182.0), 59	ns
Biochemistry at initial diagnosis			
UFC (µg/24 h)	423 (1083), 13	498 (435), 26	ns
DXM (µg/dL)	21.7 (29.6), 7	23.3 (12.2), 25	ns
Morning plasma cortisol (µg/dL)	15.7 (59.1), 14	21.7 (12.6), 32	ns
Clinical evaluation at follow-up			
Systolic blood pressure (mmHg)	130 (24), 21	129 (21), 59	ns
Diastolic blood pressure (mmHg)	82 (12), 21	82 (16), 59	ns
HbA1c (%)	5.9 (0.9), 19	6.0 (1.0), 59	ns
Cholesterol (mg/dL)	208 (71), 19	212 (52), 59	ns
LDL (mg/dL)	132 (57), 19	130 (46), 58	ns
Triglycerides (mg/dL)	108 (58), 19	111 (92), 59	ns
T-Value in DXA	-1.8 (2.4), 11	-1.1 (1.5), 44	ns
BMI (kg/m ²)	28.6 (8.7), 21	26.1 (5.5), 59	ns
Waist-to-hip ratio	0.89 (0.19), 20	0.92 (0.10), 58	ns
Grip strength (%)*	92.1 (42.4), 18	89.3 (30.9), 58	ns
Chair rising test (s)	7.0 (4.0), 19	7.0 (4.0), 55	ns

*Grip strength was assessed with a hand dynamometer; mean values of three trials of the leading hand were compared to mean values of an age- and gender-matched normative population (=100%).

BMI, body mass index; DXA, dual energy X-ray absorptiometry; DXM, serum cortisol after 1 mg dexamethasone; UFC, urinary free cortisol.

hydrocortisone replacement therapy on QoL (data not shown). Regarding ECS patients with different surgical approaches, there was no significant difference between

QoL results of patients that underwent BADx and those with ongoing functional activity of their adrenal glands (data not shown).

Table 4 Health-related quality of life (QoL) in patients with ectopic Cushing's syndrome (ECS) and Cushing's disease (CD) according to gender. Data are presented as median (IQR), *n*.

	Females		<i>P</i>	Males		<i>P</i>
	ECS	CD		ECS	CD	
Age at follow-up in years	65 (27), 11	51 (17), 40	ns	55 (31), 7	50 (27), 11	ns
Time from first symptoms until remission in months	44 (111), 10	43 (111), 36	ns	9 (35), 7	72 (45), 8	0.029
Time from diagnosis until remission in months	1.0 (33.0), 11	3.5 (36.0), 40	ns	1.0 (23.0), 7	2.0 (54.0), 11	ns
Follow-up time since remission in months	126 (110), 11	104 (146), 40	ns	66 (28), 7	216 (384), 11	ns
Biochemical and clinical evaluation						
UFC (µg/24 h) at diagnosis	352 (810), 7	511 (315), 19	ns	944, 3	1347, 3	ns
BMI (kg/m ²)	32.4 (8.9), 11	27.0 (8.1), 40	ns	25.0 (5.6), 7	25.4 (3.5), 11	ns
Waist-to-hip-ratio	0.89 (0.1), 11	0.91 (0.1), 40	ns	0.99 (0.24), 7	0.98 (0.13), 11	ns
Quality of life assessment						
SF-36 physical functioning	55 (30), 11	78 (53), 40	ns	75 (35), 7	95 (40), 11	ns
SF-36 role-physical	88 (75), 10	50 (100), 40	ns	50 (100), 7	100 (31), 10	ns
SF-36 bodily pain	90 (60), 11	68 (67), 40	ns	90 (33), 7	90 (44), 11	ns
SF-36 general health	60 (45), 11	45 (40), 39	ns	65 (20), 7	60 (50), 11	ns
SF-36 vitality	60 (15), 11	40 (25), 39	0.033	50 (45), 7	50 (45), 11	ns
SF-36 social functioning	75 (50), 11	63 (38), 40	ns	100 (25), 7	88 (25), 11	ns
SF-36 role-emotional	100 (36), 10	67 (100), 40	0.043	100 (100), 7	100 (100), 11	ns
SF-36 mental health	92 (30), 9	64 (32), 40	0.010	84 (41), 6	72 (25), 10	ns
Cushing QoL	73 (18), 11	59 (36), 38	0.030	73 (65), 7	75 (44), 11	ns
Tuebingen CD-25 total score	17 (23), 8	25 (39), 34	ns	17 (32), 6	38 (60), 9	ns

BMI, body mass index; SF-36, Short Form (36) Health Survey: higher scores indicate better QoL; Cushing QoL, higher scores indicate better outcome; Tuebingen CD-25, lower scores indicate better QoL; UFC, urinary free cortisol.

Discussion

Long-term outcome of ECS is difficult to analyze, as the underlying etiology varies substantially and tumor-related mortality is high. Here, we present for the first time a structured follow-up of long-term survivors of ECS patients and compare these data with those of patients with CD in remission.

The main findings of our study are:

Firstly, long-term outcome of survivors of ECS is acceptable with regard to cardiovascular, metabolic and musculoskeletal comorbidities and overall equivalent to that of patients with CD.

Secondly, during the active phase of hypercortisolism, self-reported psychiatric morbidity in ECS patients is high and statistically not different from CD, whereas long-term psychiatric morbidity is lower and health-related QoL is better in ECS compared to CD.

It has well been appreciated, that both health-related and disease-specific QoL is more frequently impaired in female than in male patients with CS (11, 12, 13, 19). Although potential differences in clinical presentation, coping strategies, illness perceptions and the long-term effects of hypercortisolism have been suggested, the reason for this gender discrepancy remains uncertain (11, 12, 13, 20, 21, 22).

With respect to our current data, the impairment of QoL in females seems to be an observation with more relevance for CD patients, as they reported worse disease-specific QoL compared to their ECS counterparts (as illustrated by significantly lower scores in the Cushing-specific questionnaire Cushing QoL). The subitems of the SF-36 questionnaire showed that female ECS and CD were comparable with regard to physical functioning or general health, whereas their results for vitality, emotional role and mental health differed significantly. Therefore, female CD patients seem to suffer from more mental disorders after remission than female ECS patients, although during active disease both groups report similar QoL (23).

This is probably not due to the initial intensity of hypercortisolism, duration of follow-up or differences in body shape (BMI and waist-to-hip ratio) as these parameters were found to be comparable between ECS and CD patients. Differences in age, gender and time since remission are probably also not responsible for the better QoL in ECS patients. This was also illustrated by a separate QoL analysis of the 21 ECS patients matched for age, gender and time since remission with 21 patients with CD, again showing significantly better quality of life in female

ECS patients (data not shown). In contrast, male ECS and CD patients showed no significant difference in QoL.

Of note, a relevant QoL impairment has already been described in presence of hypopituitarism (24, 25, 26, 27, 28, 29). As the latter was rather prevalent in our control group of patients with cured CD, this might have contributed to their unfavorable QoL results. Nevertheless, glucocorticoid substitution did not seem to play a major role in our current cohort, as a comparable frequency of female ECS and CD patients received hydrocortisone at the time of follow-up examination. Interestingly, however, a more recent investigation of subjects with various hypothalamic-pituitary-adrenal (HPA) axis dysregulations (i.e. CD, adrenal CS and adrenal insufficiency) showed that health-related QoL appears significantly impaired in the context of all forms of HPA alterations, with the most negative influences derived from hypercortisolism and with the worst results observed in patients suffering from CD (30).

Apart from hypopituitarism, a prolonged recovery from relevant comorbidities associated with initial hypercortisolism may have contributed to the impaired QoL detected in our current cohort. For instance, it has been frequently shown that even if psychopathology (31, 32), myopathy (15) and cardiovascular impairment (33, 34, 35, 36) may improve over time, complete restitution may not be achieved (15). Finally, the potential impact of an (at least temporally) glucocorticoid withdrawal syndrome needs to be considered (37). All of these aspects do not only reveal the broad devastating potential of glucocorticoid excess but may also explain why QoL is especially lowered in the early phase of remission. Further studies are needed to clarify the distinct pathological impact of these factors.

An important limitation of the study is the fact, that a small, heterogeneous group of patients with ECS is compared to patients with pituitary-dependent CS. Several pre- and postoperative circumstances may largely differ, although we did not observe significant differences regarding biochemistry or comorbidities at initial diagnosis.

For patients with QoL assessment, UFC levels at baseline were not significantly higher in patients with ECS compared to CD patients. This is in contrast to earlier series, where UFC levels were higher in ECS (38). Our finding might be due to a selection bias as QoL assessment was only performed in long-term-surviving patients. For all ECS patients median of UFC was 796 µg/24 h (IQR: 1427) compared to 498 µg/24 h (IQR: 435) in CD ($P=ns$).

In the Cushing QoL and some subitems of the SF-36, significant differences between female ECS and CD patients were observed. In contrast, this was not the case for the Tuebingen CD-25. This might either be due to a lower patient number or topics exclusive to the Tuebingen CD-25 questionnaire (e.g. sexuality and eating behavior).

In summary, our data are in line with the concept that patients with CD have a longer time between first symptoms and diagnosis than ECS patients resulting in a longer exposure to excessive cortisol levels. This appears to affect mental health and health-related QoL, but not cardiovascular, metabolic and bone health. These findings support the theory that CS has to be diagnosed and treated as early as possible.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

This work is part of the German Cushing's Registry CUSTODES and has been supported by a grant from the Else Kröner-Fresenius Stiftung to M R (2012_A103 and 2015_A228). Additionally, T D received a grant from the Interdisciplinary Center for Clinical Research (IZKF) of the University of Würzburg (grant number Z-2/57).

Acknowledgments

This study was only feasible due to the support of the Cushing Registry teams in Munich (Sabrina Hierse and Stephanie Zopp) and Würzburg (Maximilian Müller, Kristina Ehrlich and Carina Roth).

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Received 19 March 2018

Revised version received 25 May 2018

Accepted 30 May 2018