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Neuropsychiatric and metabolic aspects of dopaminergic therapy in neuroendocrine disease

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1. List of abbreviations

PitNETs: pituitary neuroendocrine tumors

NFPA: non-functioning pituitary adenomas

DA: dopamine agonists

ICD: impulse control disorders

PD: Parkinson’s disease

P-gp: P-glycoprotein

HRQOL: health-related quality of life

EPQ-RK: Eysenck personality questionnaire

TPQ: Tridimensional Personality Questionnaire devised by Cloninger

DRD2: dopamine receptor D2 gene

SAI: secondary adrenal insufficiency

SF-36: Short Form Survey

BDI: Beck's Depression Inventory

STAI: State-Trait Anxiety Inventory

ESS: Epworth Sleepiness Scale

PSQI: Pittsburgh Sleep Quality Index

BMI: body mass index

2. Introduction

Pituitary neuroendocrine tumors (PitNETs) are generally benign tumors with complex clinical characteristics related to hormone hypersecretion and/or growing sellar tumor mass. The majority arise from the hormone-secreting adenohypophysial cells that are members of the family of neuroendocrine epithelial cells. They are classified into seven morphofunctional types accroding to the pituitary cells of the anterior pituitary they arise from: lactotroph, somatotroph, thyrotroph, corticotroph or gonadotroph, null cell or immunonegative tumor and plurihormonal tumors.

Epidemiologic studies show that pituitary adenomas are rare but seem to have an increasing incidence (between 3.9 and 7.4 cases per 100.000 per year) and prevalence (76 to 116 cases per 100.000 population) in the general population (approximately 1 case per 1000 of the general population). Most new cases diagnosed are prolactinomas and non-functioning pituitary adenomas (NFPA) (*Daly et al, 2020*). Hormonal excess syndromes due to PitNETs, even if being rare, have a broad clinical presentation including symptoms resulting from the hormonal excess depending on the hormone overproduction, symptoms due to the pituitary insufficiency and symptoms resulting from the pituitary mass per se.

It is also increasingly recognized that patients with hormonal excesses suffer from neuropsychiatric side-effects, not only due to the neuroanatomic position of the pituitary mass itself but probably also due to their medical treatment. More specifically, patients with prolactinomas, that are the most common pituitary adenomas and account for about 40% of all pituitary tumors, are being usually treated with so called dopamine agonists (DA) such as cabergoline (*Melmed et al., 2011*). The most common side effects under cabergoline include gastrointestinal symptoms, postural hypotension, dizziness and headaches. Apart from these common side effects, some other, rarer central side effects such as impulse control disorders

(ICD) (i.e. pathological gambling, compulsive shopping, hypersexuality and binge eating) have been recently reported, especially in Parkinson's disease (PD) patients, that are also treated with DA with a prevalence up to 17.1% with patients under DA showing a 2- to 3.5-fold increased risk of developing an ICD (*Weintraub et al., 2010*). Even if the doses of DA used in these instances are considerably smaller (5 to 10 times) than those used to treat PD, distinct dopaminergic personality patterns have been already described in patients with prolactinomas. However, these rare central side effects have not been systematically investigated yet. There are only a few small studies in this field. The total prevalence of ICD seems to be significantly higher in patients with prolactinomas (24.6% referring to the prevalence of one or more ICD) compared to the NFPA group (17.14%) or the general population (8.4%), predominantly with an increased rate of hypersexuality (*Viana et al., 2012, Bancos et al., 2014*). These symptoms are generally characterised by the maladaptive nature of the preoccupations and the inability to control these urges and mainly have a de novo onset after the initiation of dopamine therapy in higher dosages. Central side effects may depend on a substance's ability to pass the blood-brain barrier, which can be actively controlled by transporter molecules such as the P-glycoprotein (P-gp) encoded by the *ABCB1* gene.

A number of studies have documented an altered psychological profile and emotional difficulties in patients with prolactinomas mainly characterized by increased anxiety, depression and impaired quality of life (K*ars et al., 2007*), changes that occasionally persist even after remission of hyperprolactinemia (*Sobrinho 1998*). Personality patterns such as extraversion and novelty seeking have been associated with an altered dopaminergic activity in healthy subjects (*Smillie et al., 2010*). Patients with prolactinomas have been described as exhibiting an altered dopaminergic tone and are often treated with DA (*Ben-Jonathan et al., 2001*). Little is known about the personality traits of this patient group.

For some years, prolactin has attracted attention as a metabolic hormone. Hyperprolactinemia has been reported to be associated with abnormalities of carbohydrate and lipid metabolism (*Ben-Jonathan et al., 2006*). Thus, to some extent the metabolic consequences of hyperprolactinemia are similar to those of the metabolic syndrome. Data implicate that dopaminergic treatment in prolactinomas that leads to normallization of prolactin, has additional metabolic effects, apart from the above mentioned neuropsychiatric side effects. It seems to trigger weight loss in some patients (*Korner et al., 2003*) by mechanisms further than the normalisation of prolactin levels but also improve lipid profile and glycemic control (*Berinder et al., 2011*).

Patients with neuroendocrine disease and PitNETs have been found to have an impaired health-related quality of life (HRQOL) due to multiple factors such as visual field defects, number of surgeries, pain, radiation therapy and co-hypopituitarism (*Andela et al., 2015, Leistner et al. 2015, Dimopoulou et al., 2014*). The individual effect of insufficient axes and replacement therapy on HRQOL has however been a matter of debate. Studies on patients with adrenal insufficiency on standard replacement showed that health-related subjective status is impaired, irrespective of origin of disease or concomitant disease (*Hahner et al., 2007*).

Apart from impaired HRQOL, patients with NFPA exhibit high morbidity and mortality rates. Growth hormone deficiency and high doses of glucocorticoid substitution therapy have been identified as corresponding risk factors (*Tampourlou et al. 2018*). Interestingly, high levels of endogenous cortisol in, e.g., patients with post-traumatic stress disorder or patients with Cushing's disease have been linked to shorter telomere length (*Aulinas et al., 2015*). Telomeres are noncoding DNA regions located at the end of chromosomes consisting of repetitive DNA sequences which shorten with ageing and hereby determine cell survival. Therefore, telomere length can serve as a predictor for the onset of disease and mortality in patients with NFPA.

The aim of the present habilitation thesis was to investigate the neuropsychiatric and metabolic aspects of dopaminergic therapy in neuroendocrine disease.

3. Objective/Questions to be answered

- Could genetic polymorphisms of the *ABCB1* gene predict central neuropychiatric side effects of cabergoline therapy in patients with prolactinomas?
- Do patients with prolactinomas experience altered personality traits compared to controls and non-functioning- pituitary adenoma patients?
- Can polymorphisms of the *ANKK1/DRD2 Taq1A* gene, which has been associated with an altered dopaminergic tone, predict weight changes under dopaminergic treatment in prolactinomas?
- Is health-related quality of life in patients with non-functioning pituitary adenomas impaired and does the dose of hydrocortison substitution play any role?
- Do patients with non-functioning pituitary adenomas have shorter telomeres and is that associated with high doses of glucocorticoids?

4. Studies carried out and main findings

4.1. Polymorphisms of the drug transporter gene *ABCB1* predict side effects of treatment with cabergoline in patients with prolactinomas (Athanasoulia et al., 2012, Eur J Endocrinol, Sep;167(3):327-35. doi: 10.1530/EJE-12-0198)

Aim/Methods

The aim of this project was to determine whether the functionality of P-gp encoded from the *ABCB1* gene is related to cabergoline levels in the brain by means of in vivo experiments with an *ABCB1ab* double knockout mouse model. Among all dopamine agonists used for the treatment of prolactinomas, we chose cabergoline as it is the gold standard medical treatment for prolactinoma patients. We further investigated whether polymorphisms in the *ABCB1* gene could predict the occurrence of central side effects in patients with prolactinomas treated with cabergoline.

- In vivo experiments using *Abcb1a* and *Abcb1b* double knockout mice

To examine whether cabergoline is a substrate of P-gp, we developed an in vivo assay using mouse mutants lacking the homologues of the human *ABCB1* gene (i.e. *ABCB1ab* double knockout mice) and used eight wild-type and eight *ABCB1ab* double knockout mice.

- Human case-control SNP association study

Adult patients diagnosed with prolactinomas with the diagnosis of a prolactinoma (micro- or macroadenomas) treated with cabergoline during the disease history were included in the study. Patients that experienced the examined symptoms or side effects under cabergoline treatment (answered with 'yes') were considered as cases and patients that did not experience these symptoms (answered with 'no' for each relevant question) as control group. The patients' central side effects were investigated with standardised and customised questionnaires that

encompassed socioeconomic and baseline characteristics and questions regarding their medical history. Clinical characteristics of the subjects were collected with regard to disease history, tumor characteristics, previous and present therapy and comorbidities.

Results

o In vivo experiments using *ABCB1ab* double knockout mice

Brain concentrations of cabergoline were ten times higher in the mutant mice compared with their wild-type littermates (data represented as an organ/plasma concentration ratio).

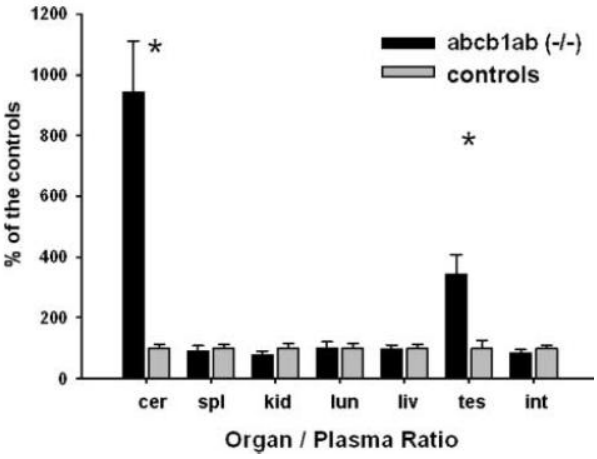

Figure 1: Blood–organ barrier function for cabergoline. Organ/plasma ratio of cabergoline concentration in *Abcb1ab*$^{(-/-)}$ mice compared with wild-type controls after s.c. administration of cabergoline for 11 days via osmotic pumps. The organ/plasma ratios are shown as percentage of the control. *Statistical significance between the knockout mutants and controls (P<0.05). cer, cerebrum; spl, spleen; kid, kidney; lun, lung; liv, liver; tes, testes; int, intestine. Values are shown as mean±S.E.M.

o Human case–control SNP association study

We asked the patients to evaluate their symptoms in terms of presence, change, enhancement, reduction or consistency under cabergoline. In the study population of 79 patients with prolactinomas treated with cabergoline, mainly central side effects/symptoms such as headaches, increased libido, depressed mood, sleep disorders, fatigue, dizziness and aggressiveness were reported under cabergoline therapy.

	Presence of symptom under cabergoline		Change of symptom under cabergoline				
			Enhancement		Reduction or consistency		
	n	%[a]	*n*	%	*n*	%	*P* value[b]
Fatigue	35 (65)[c]	53.8	16	24.2	50	75.8	<0.001
Headaches	26 (64)	40.6	10	15.4	55	84.6	0.001
Sleep disorders	26 (65)	40	11	17.2	53	82.8	<0.001
Dizziness	22 (64)	34.4	7	10.9	57	89.1	<0.001
Decreased libido	18 (66)	27.3	6	9.2	59	90.8	<0.001
Increased libido	16 (65)	24.6	16	25.8	46	74.2	<0.001
Depressed mood	26 (65)	40	12	18.2	54	81.8	<0.001
Aggressiveness	17 (65)	26.2	7	10.6	59	89.4	<0.001
Anxiety	19 (64)	29.7	7	10.9	57	89.1	<0.001
Visual hallucinations	2 (65)	3.1	1	1.5	64	98.5	0.031
Gambling	1 (65)	1.5	1	1.5	64	98.5	0.015
Compulsive shopping	5 (65)	7.7	2	3.1	63	96.9	0.005

[a]Percentage of cases in the group of patients that answered the question.
[b]χ^2 between presence and change of symptom under cabergoline (enhancement or reduction and consistency of symptom).
[c]The total number of patients that answered the question is given in parenthesis (cases and controls).

Table 1: central side effects in patients with prolactinomas under cabergoline treatment

Four *ABCB1* SNPs were genotyped in all patients. SNPs were selected from dbSNP (http://www.ncbi.nlm.nih.gov:80/) according to previously published data that revealed altered expression and function of the P-gp.

SNP	Chromosomal position	Genomic localisation	Map-pos	Alleles	HWE	MAF	Call rate
ABCB1							
rs1045642	7	Exon 26	87138645	C/T	0.65	0.44	1.00
rs2032582	7	Exon 21	87160618	G/T	1.00	0.47	1.00
rs2032583	7	Intron 21	87160561	C/T	0.68	0.16	1.00
rs2235015	7	Intron 4	87199564	G/T	0.49	0.20	1.00

HWE, *P* values of the Hardy–Weinberg equilibrium test; MAF, minor allele frequency.

Table 2: Information on genotyped SNPs of ABCB1 gene. Chromosomal positions are given according to the February 2009 (hg19) human reference sequence database of the International Human Genome Sequencing Consortium.

In the carrier model, the carrier of a specific nucleotide was compared with the non-carrier. In the allelic model, each nucleotide was evaluated having a twofold higher effect in the genotype, whereas in the heterozygous vs homozygous genotype model, each SNP was compared. We found that the SNP rs1045642 had an influence on two side effects under cabergoline: fatigue and sleep disorders. More specifically, significant effects were observed

for the C-carriers of rs1045642 that presented less frequent fatigue under cabergoline in comparison with non-C-carriers (Pwycor=0.04, OR=0.23). Additionally, the heterozygous CT individuals presented less frequent sleep disorders in comparison with homozygous CC or TT (Pwycor=0.02, OR=0.20).

Conclusion

In conclusion, this study was the first to demonstrate that individual *ABCB1* gene polymorphisms, reflecting a different expression and function of the P-gp, could predict the occurrence of central side effects under cabergoline. Our findings can be viewed as a step into personalised therapy in patients with prolactinomas.

4.2. Distinct dopaminergic personality patterns in patients with prolactinomas: a comparison with nonfunctioning pituitary adenoma patients and age- and gender-matched controls (Athanasoulia et al., 2012, Neuroendocrinology;96(3):204-11. doi: 10.1159/000335996)

Aim/Methods

Personality patterns such as extraversion and novelty seeking have been associated with an altered dopaminergic activity in healthy subjects. Patients with prolactinomas have been described as exhibiting an altered dopaminergic tone and are often treated with DA. Little is known about the personality traits of this patient group. Hence, we aimed at examining whether patients with prolactinomas exhibit modified personality patterns compared to patients with NFPA and healthy controls.

In this cross-sectional study, 86 patients with prolactinomas and 58 patients with NFPA were compared with 172 mentally healthy age- and gender-matched controls. To assess personality traits, standardized personality questionnaires (Eysenck personality questionnaire-EPQ-RK and Tridimensional Personality Questionnaire devised by Cloninger-TPQ) were administered.

Results

Patients with either prolactinomas or NFPA showed a distinct personality profile compared to the normal population, characterized by increased neuroticism, and they also answered in a socially desirable mode. On harm-avoidant total and subscales, they presented with a higher fear of uncertainty and also increased fatigability and asthenia. The prolactinoma patients, when contrasted with the 'clinical' control group of patients with NFPA and after post hoc tests for multiple comparisons following the Bonferroni-Holm procedure showed significantly reduced extraversion and increased shyness with strangers tending to be more neurotic and present lower scores in the novelty seeking subscale impulsiveness.

	Controls normal population (1)		Nonfunctioning pituitary adenoma patients (NFPA) (2)		Patients with prolactinoma (3)		ANCOVA	Bonferroni-Holm corrected post hoc tests		
	mean	SD	mean	SD	mean	SD	p value	p value (1 vs. 2)	p value (1 vs. 3)	p value (2 vs. 3)
Eysenck Personality Questionnaire (EPQ-RK)										
Psychoticism (EPQ-P)	1.89	1.55	1.35	1.46	1.83	1.74	n.s.	n.s.	n.s.	n.s.
Extraversion (EPQ-E)	6.70	3.31	5.91	3.84	5.33	3.44	**<0.005**	n.s.	**<0.006**	**0.044**
Neuroticism (EPQ-N)	3.06	2.48	4.02	2.80	5.09	3.12	**<0.001**	**<0.045**	**<0.001**	*0.056*
Social desirability (EPQ-SD)	3.41	2.36	5.76	2.76	4.99	2.88	**<0.001**	**<0.001**	**<0.001**	n.s.
Cloninger Temperament and Personality Questionnaire (TPQ)										
TPQ novelty-seeking total (TPQ-N.S.)	15.38	4.83	13.49	4.83	13.21	4.72	**<0.001**	n.s.	**<0.001**	n.s.
Exploratory excitability (TPQ-N.S.1)	4.26	1.78	3.65	1.83	3.52	1.88	**<0.006**	n.s.	**<0.003**	n.s.
Impulsiveness (TPQ-N.S.2)	3.66	1.87	3.44	2.12	2.91	1.81	**<0.009**	n.s.	**<0.009**	*0.072*
Extravagance (TPQ-N.S.3)	4.09	1.56	3.37	1.50	3.46	1.63	**<0.008**	n.s.	**<0.006**	n.s.
Disorderliness (TPQ-N.S.4)	3.37	1.78	3.0	1.57	3.30	1.78	**<n.s.**	n.s.	n.s.	n.s.
TPQ harm avoidance total (TPQ-HA)	11.51	5.27	15.63	6.81	17.35	6.84	**<0.001**	**<0.001**	**<0.001**	n.s.
Anticipatory worries and pessimism (TPQ-HA1)	3.60	2.14	4.25	2.49	4.77	2.53	**<0.001**	n.s.	**<0.001**	n.s.
Fear of uncertainty (TPQ-HA2)	3.78	1.75	4.40	1.82	4.78	1.79	**<0.001**	*0.052*	**<0.001**	n.s.
Shyness with strangers (TPQ-HA3)	2.12	1.73	2.83	1.86	3.53	2.06	**<0.001**	**<0.049**	**<0.001**	**0.044**
Fatigability and asthenia (TPQ-HA4)	2.01	1.76	4.14	2.66	4.21	2.51	**<0.001**	**<0.001**	**<0.001**	n.s.
TPQ reward dependence total (TPQ-RD)	17.17	4.47	15.56	3.69	16.78	3.99	n.s.	n.s.	n.s.	n.s.
Sentimentality (TPQ-RD1)	3.92	1.13	3.95	1.17	3.94	1.14	n.s.	n.s.	n.s.	n.s.
Persistence (TPQ-RD2)	3.92	2.00	3.54	1.86	3.95	1.94	n.s.	n.s.	n.s.	n.s.
Attachment (TPQ-RD3)	6.55	2.61	5.70	2.28	6.01	2.60	n.s.	n.s.	n.s.	n.s.
Dependence (TPQ-RD4)	2.79	1.39	2.37	1.41	2.92	1.37	n.s.	n.s.	n.s.	n.s.

Results of the Eysenck personality questionnaire (EPQ-RK) and the Cloninger temperament and personality questionnaire (TPQ) are compared between groups using ANCOVA adjusted for age and gender, hypertension and diabetes mellitus. Bonferroni-Holm-corrected post-hoc tests for two group comparisons were performed in the case of significant differences in the global ANCOVA. Note: Significant effects are in bold type. Marginal effects ($p < 0.08$) are presented in italics.

Table 3: Personality traits according to the Eysenck Personality Questionnaire (EPQ-RK) and Cloninger Temperament and Personality Questionnaire (TPQ) in the three study groups

Conclusion

This is, to our knowledge, the first study providing new evidence of an altered personality profile of prolactinoma patients which might affect the patient-doctor relationship, treatment and patient's quality of life.

4.3. The effect of the ANKK1/DRD2 Taq1A polymorphism on weight changes of dopaminergic treatment in prolactinomas (Athanasoulia et al., 2014, Pituitary, 17:240–245. doi: 10.1007/s11102-013-0496-y)

Aim/Methods

Treatment with DA in patients with prolactinomas has been associated with weight loss in short term studies. However, long-term studies on weight changes are lacking. Taq1A is a restriction fragment length polymorphism considered as a gene marker for the dopamine receptor D2 gene (*DRD2*). The presence of at least one A1 allele is linked to reduced brain dopaminergic activity due to reduced receptor binding and lower density of the dopamine 2 receptor. We aimed at testing the hypothesis that the dopaminergic treatment in prolactinoma patients leads to sustained weight loss and that the presence of diminished weight loss response under dopamine agonists is associated with the minor A1 allele of *Taq1A*.

Results

We included 44 patients with prolactinomas treated with DA. Outcome measures were weight and body mass index (BMI) change under dopaminergic treatment after two years with regard to *Taq1A* status and sex. We observed that the dopaminergic treatment leads to a significant mean weight loss of 3.1±6.25 kg.

Regarding *Taq1A* polymorphisms, 21 patients were carriers of at least one A1 allele and 23 patients had a genotype of A2/A2. However, the presence of the A1 allele was neither associated with the mean BMI at baseline nor with an altered weight loss response under DA therapy.

	Mean	SD	*p* value
Weight after treatment (T2) (kg)	75.45	19.72	0.002*
BMI after treatment (T2) (kg/m^2)	25.19	5.77	0.002**
Delta weight (kg)	−3.1	6.25	
Percent of weight loss (%)	3.48	7.78	
Percent of weight loss in regard to gender (%)			
In male	6.65	7.87	0.030
In female	1.48	7.17	
Percent of weight loss in regard to BMI at T0 (%)			
In normal weight subjects	1.82	8.2	NS
In overweight and obese subjects	5.3	7.04	

	N	%
Subjects with weight loss ≥5 % and <10 % of initial weight	13	29.5
Subjects with weight loss ≥10 % of initial weight	8	18.2
In the overweight and obese group (n = 21)[a]		
Subjects with weight loss ≥ 5 % and < 10 % of initial weight	7	33.3
Subjects with weight loss ≥ 10 % of initial weight	5	23.8

	+A1[b]		−A1[c]		*p* value
	Mean	SD	Mean	SD	
Weight and BMI in regard to the A1 allele of the *Taq1A*					
Weight after treatment (T2) (kg)	77.43	16.67	73.64	22.36	NS
BMI after treatment (T2) (kg/m^2)	25.42	5.03	24.98	6.47	NS
Delta weight (kg)	−3.57	6.04	−2.67	6.54	NS
In male	−6.3	6.34	−5.57	7.91	NS
In female	−1.09	4.74	−1.4	5.66	NS

Table 4: Weight and BMI after two years of dopaminergic treatment (TO: baseline, T2: two years after initiation of tretment), NS non-significant, * p value weight at baseline (T0) versus weight after treatment (T2) ** p value BMI at baseline (T0) versus BMI after treatment (T2) a According to BMI at baseline (T0) b Presence of at least one A1 allele c Absence of A1 allele

Conclusion

Our results implicate that the dopaminergic treatment leads to a sustained weight loss in patients with prolactinomas after 2 years. However, there was no association to the A1 allele of *Taq1A*, an observation that needs to be analysed in larger cohorts.

4.4. Health-related quality of life in patients with non-functioning pituitary adenoma: A special focus on hydrocortisone replacement dose (Wild et al., 2020, Qual Life Res Dec;29(12):3325-3331. doi: 10.1007/s11136-020-02582-7)

Aim/Methods

Patients with NFPA suffer from pronounced impairments in physical and mental measures that lead to an impairment of HRQOL. The individual effects of insufficient axes and replacement therapy on HRQOL has however been a matter of debate. Studies on patients with adrenal insufficiency on standard replacement showed that health-related subjective health status is impaired, irrespective of origin of disease or concomitant disease (*Hahner et al., 2007*). Especially for secondary adrenal insufficiency (SAI) due to pituitary adenoma data are conflicting. Some authors described an impaired HRQOL associated with higher hydrocortisone doses. The primary aim of this study is to assess the HRQOL in patients with NFPA in terms of presence of SAI and in patients without SAI and the secondary to explore the impact of treatment parameters such as daily hydrocortisone dose.

Results

In a cross-sectional study we evaluated parameters of HRQOL in 95 patients with NFPA using standardised questionnaires like Short Form (SF-36), Beck's Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI), Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI) and a self-constructed questionnaire about medical history.

Total health (sum) score could be computed for 80 (84.2%) patients and was 67.2 ± 20.6. We could not find any significant difference between patients with and without SAI in the standardised questionnaires in terms of HRQOL. In order to investigate which parameters played a significant role with regard to HRQOL, we conducted an explorative correlation analysis. Following parameters were correlated with SF-36 sum scores: female sex, body-mass-

index (BMI), irradiation (yes, no), gonadotropic gonadotropin insufficiency (yes, no), overt growth hormone deficiency (yes, no), daily dose of hydrocortisone in mg, PSQI, ESS, BDI and STAI sum scores. In a further regression analysis, we could show that female sex was negatively correlated with SF-36 global health (b=-0.465; p=0.045), as well as daily dose of HC substitution regardless of using BDI or STAI in the block (b=-0.397; p=0.021, b=-0.390; p=0.016 respectively). SF-36 physical health was negatively influenced by female sex, BMI, BDI and daily dose of hydrocortisone substitution.

	SF-36 global health		SF-36 physical health		SF-36 mental health	
	β	p (variable)	β	p (variable)	β	p (variable)
Age	−0.114	0.547	−0.187	0.292	−0.013	0.948
Female sex	**−0.465**	**0.045**	**−0.531**	**0.014**	−0.389	0.098
BMI	−0.407	0.076	**−0.489**	**0.023**	−0.262	0.259
Impaired visual field defects	0.230	0.284	0.322	0.236	0.253	0.229
Number of insufficient pituitary axes	0.086	0.693	0.039	0.848	0.156	0.480
Surgery	−0.060	0.776	−0.028	0.885	**−0.385**	**0.047**
Irradiation	0.146	0.481	0.215	0.258	0.196	0.211
PSQI	−0.272	0.180	−0.215	0.359	−0.323	0.114
ESS	0.142	0.439	0.060	0.768	0.179	0.328
BDI	**−0.489**	**0.006**	−0.347	0.073	**−0.543**	**0.005**
Daily dose of hydrocortisone	**−0.397**	**0.021***	**−0.403**	**0.038**	−0.252	0.142

Significant effects are presented in bold

*The difference remained statistical significant even after replacing BDI with STAI, $\beta = -0.397$; $p = 0.021$, $\beta = -0.390$; $p = 0.016$, respectively

Table 5: Independent factors influencing the SF-36 global, physical and mental health score in patients with SAI

Conclusion

Taken together, NFPA patients with SAI do not have a worse HRQOL than patients with NFPA and intact corticotropic axis. We could show that higher doses of hydrocortisone are associated with an impaired HRQOL measured by SF-36 global and physical health score, whereas mental health score is not significantly influenced by the hydrocortisone dose. This detected negative correlation of higher hydrocortisone dose on HRQOL could reflect the negative influcence of higher hydrocortisone dose on the general health score including metabolism and myopathy. Alternatively it could be correlated with the common practice of some physicians to increase the hydrocortisone dose in patients with physical complaints attempting to normalize them.

4.5. Shorter telomeres associated with high doses of glucocorticoids: the link to increased mortality? (Athanasoulia-Kaspar et al., 2018, Endocr Connect. Aug 1;7(11):1217-1226. doi: 10.1530/EC-18-0362)

Aim/Methods

Patients with NFPA exhibit high morbidity and mortality rates. Growth hormone deficiency and high doses of glucocorticoid substitution therapy have been identified as corresponding risk factors. Interestingly, high levels of endogenous cortisol in, e.g., patients with post-traumatic stress disorder or patients with Cushing's disease have been linked to shorter telomere length. Telomeres are noncoding DNA regions located at the end of chromosomes consisting of repetitive DNA sequences which shorten with ageing and hereby determine cell survival. Therefore, telomere length can serve as a predictor for the onset of disease and mortality in some endocrine disorders (e.g., Cushing's disease). We examined telomere length from blood in patients (n = 115) with NFPA in a cross-sectional case control (n = 106, age-, gender-matched) study using qPCR. Linear regression models were used to identify independent predictors of telomere length.

Results

We showed that patients with NFPA exhibited shorter telomeres than controls. No significant association of indices of growth hormone deficiency (IGF-1-level-SDS, years of unsubstituted growth hormone deficiency etc.) with telomere length was detected. Interestingly, linear regression analysis showed that hydrocortisone replacement dosage in patients with adrenal insufficiency (n = 52) was a significant predictor for shorter telomere length ($\beta = 0.377$; $p = 0.018$) independent of potential confounders. Median split analysis revealed that higher hydrocortisone intake (> 20 mg) was associated with significantly shorter telomeres.

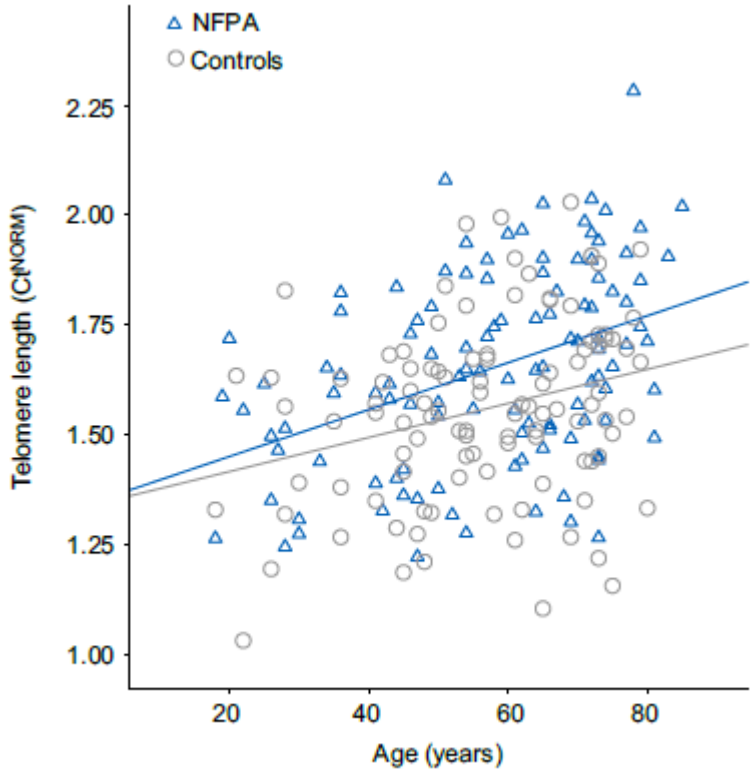

Figure 1: Shorter telomere length in NFPA patients. Correlation of adjusted pPCR values (Ct) with age in NFPA patients (n = 115) and controls (n = 106). Note, higher Cts are indicative of shorter telomeres. Pearson correlation: r = 0.404, P ≤ 0.001 (NFPA) and r = 0.282, P = 0.003 (controls). Ct, threshold cycle.

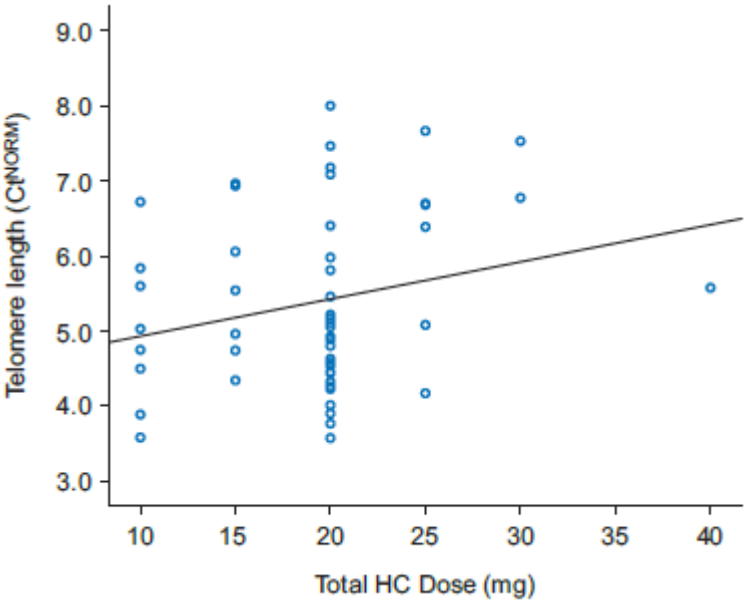

Figure 2: Telomere length in NFPA depends on the dose of glucocorticoid replacement therapy. Correlation of adjusted pPCR values (Ct) with daily total hydrocortisone dose in NFPA patients with adrenal insufficiency (n = 52). Note, higher Cts are indicative of shorter telomeres. Pearson correlation: ß = 0.060, P = 0.091. Ct, threshold cycle.

Conclusion

In this study we could demonstrate that patients with NFPA exhibit shorter telomeres than controls and that telomere shortening per year of age seems to be accelerated in these patients. Interestingly, among patients with pituitary insufficiencies, there was a clear association of higher hydrocortisone doses with shorter telomere length. To the best of our knowledge, this is the first study to evaluate telomere length in patients with NFPA. These observations strengthen the importance of adjusted glucocorticoid treatment in NFPA patients with respect to morbidity and mortality rates.

5. Discussion

The studies presented herein had as a common initiating point the need to further elucidate the complex topic of neuropsychiatric and metabolic aspects of dopaminergic treatment in patients with neuroendocrine disease and more specifically pituitary adenomas.

In our studies we could show for the first time that cabergoline is a substrate of the transporter molecule P-gp at the level of the blood–brain barrier in an experimental mouse model. Up to our study, many different moleculs such as antidepressants have been identified to be a substrate of P-gp. Going a step further, we showed that this fact has major clinical consequences for cabergoline-treated humans, insofar that genetic variants of the *ABCB1* gene, which encodes the P-gp, account for differences in the central side effects of cabergoline, most likely by influencing its concentration in the brain.

Previous studies in the field of depression treatment reported that the C-variant of SNP rs1045642 and G-variant of SNP rs2032582 were associated with higher P-gp expression and function and, therefore, poor response to antidepressants (*Kato et al., 2007*). These latest results are in accordance with our findings. We reported fewer central side effects under cabergoline in those individuals that have the 'protective' genotype mentioned above. Nevertheless, our study was focused on the evaluation of some specific genetic predictors of the *ABCB1* gene. We suppose that there are further transporting molecules and genetic pathways that influence the metabolism and action of cabergoline in the brain circulation, and further studies need to be conducted to elucidate these mechanisms.

In terms of psychopathology, our study in personality patterns found that patients with neuroendocrine disease showed a distinct personality profile compared to the mentally healthy age- and gender-matched control group. More specifically, patients with pituitary lesions appeared to be more neurotic, tending to experience negative emotional stress and answered

in a more socially desirable mode, indicating that respondents replied in a manner that will be viewed favorably by others. On harm-avoidant total and subscales they presented with a higher fear of uncertainty and increased fatigability and asthenia, but also reduced novelty seeking. These findings support the available literature and similar studies in acromegaly and NFPA, indicating that patients with pituitary lesions demonstrate distinct personality patterns in terms of increased neuroticism, fear of uncertainty, fatigability and asthenia (*Sievers et al., 2009*).

Not only psychopathology but also metabolic aspects of dopaminergic treatment were examined in the present thesis. Our innovative results could show that the prevalence of *Taq1A*, a polymorphism considered as a gene marker for the density of the dopamine-2-receptor linked to altered brain dopaminergic activity due to reduced receptor binding and lower density of the dopamine 2 receptor, could be associated with a different metabolic profile and reduced weight loss response under DA. In our cohort we observed that continuous two-year dopaminergic treatment led to a significant mean weight loss regardless of the *Taq1a* status (*Athanasoulia et al., 2014*). The exact pathopysiological mechanism of this phenomenon has not be elucidated so far. The normalisation of hyperprolactinemia and the restoration of hypogonadism has been speculated whereas the reduction of prolactin levels did not directly correlate with changes in serum leptin levels and BMI, suggesting that changes in prolactin levels are not the predominant determinant of changes in body weight (*Doknic et al., 2002)*. Another possibly important clue in the pathophysiology of weight loss under DA could be the increase of the dopaminergic tone that could lead to weight loss by further unknown mechanisms apart from reducing hyperprolactinemia (*Doknic et al., 2002)*.

In terms of HRQOL and taking more specific look in the influence of the corticotropic axis, we could show that NFPA patients with SAI do not have a worse HRQOL than patients with NFPA and intact corticotropic axis. However, higher doses of hydrocortisone were in our study

associated with an impaired HRQOL measured by SF-36 global and physical health score, whereas mental health score was not significantly influenced by the hydrocortisone dose. This result can however still not answer the question regarding causality and our results allow two explanations. First, that a higher HC dose leads to reduced HRQOL in patients with NFPA. It is well documented that a higher HC dose is being associated in the short term with increased vitality but in the long term with 'Cushingoid' side effects including muscle myopathy, osteoporosis and metabolic complications (*Popp et al., 2019*). Alternatively our observation could reflect the common practice of some clinicians to increase the HC dose in order to relieve symptoms and complaints regarding physical functioning. The HC substitution dose seems, in a further step, not only to be correlated with an impaired HRQOL but also to shorter telomere length. Telomere length serves as an early predictor of disease onset and all-cause mortality for numerous diseases, also as showed in our study in NFPA.

6. Summary and conclusions

Summarizing, the studies described in the present thesis contribute to enlighten that patients with neuroendocrine disease present a unique neuropsychiatric and metabolic profile under dopaminergic treatment.

Specific genetic polymorphisms of the transporter molecule P-gp control the intracerebral bioavailability of cabergoline and could predispose for fatigue, sleep disorders and dizziness under cabergoline. This is the first study showing that *ABCB1* gene polymorphisms could account for the occurrence of central side effects of this systematically administered medication, leading to an individual's central side effect profile. This could lead in the future to an adaptation of the treatment of individual patients. Furthermore our data provide new evidence of an altered personality profile of prolactinoma patients which might affect the patient-doctor relationship, treatment and patient's quality of life. The metabolic aspects of dopaminergic treatment suggesting that dopaminergic treatment is beneficial in terms of weight loss in patients with prolactinomas should be also taken into consideration when treating prolactinoma patients. Our observations in terms of quality of life strengthen the importance of adjusted glucocorticoid treatment in NFPA patients with respect to morbidity and mortality rates. Taken together our data show that patients with neuroendocrine disease experience an altered neuropsychiatric and metabolic profile under dopaminergic treatment and that dopamine and prolactin play a crucial role both in the regard and metabolic system. Prospective randomized studies could answer open questions about causality of dopaminergic treatment and further neuropsychiatric and metabolic aspects.

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8. Own publications

8.1. Original publications with first or last authorship in peer-reviewed journals (in chronological order)

1. Sleep patterns in patients treated for non-secreting intra- and parasellar tumors: A self-report case-control study. Carl M. Wild, Mareike Stieg, Günter K. Stalla, Caroline Jung-Sievers, Matthias K. Auer, **Anastasia P. Athanasoulia-Kaspar,** Frontiers in Endocrinology 2022 accepted for publication (8.11.2022)

2. Health-related quality of life in patients with non-functioning pituitary adenoma: A special focus on hydrocortisone replacement dose. Carl Mathis Wild, Mareike Stieg, Günter K. Stalla, Matthias K. Auer* and **Anastasia P. Athanasoulia-Kaspar* *shared last authorship,** Quality of Life Research 2020 doi: **10.1007/s11136-020-02582-7**

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1. Computer vision technology in the differential diagnosis of Cushing's syndrome. Popp KH; Kosilek RP, Frohner R, Stalla GK; **Athanasoulia-Kaspar AP**; Berr CM, Zopp S, Reincke M, Witt M; Würtz RP; Deutschbein T; Quinkler M; Schneider HJ, Exp Clin Endocrinol Diabetes. 2019 doi: 10.1055/a-0887-4233

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8.6. Other publications

1. Young women with Ullrich-Turner syndrome. Recommendations of an expert workshop on the transition to adult medicine [Junge frauen mit Ullrich-Turner-syndrom. Empfehlungen eines expertenworkshops zum Übergang in die Erwachsenenmedizin] Stalla, GK, **Athanasoulia, AP**, Führer, D, Frank-Herrmann, P, Oppelt, PG, Hauffa, BP, Dörr, HG Gynäkologe 2014 · 47:135–144 DOI 10.1007/s00129-013-3320-x Online publiziert: 31. Januar 2014 © Springer

2. Transition of young women with Ullrich-Turner syndrome to adult medicine: Current recommendations of an expert workshop [Transition von jungen Frauen mit Ullrich-Turner-Syndrom in die Erwachsenenmedizin: Aktuelle Empfehlungen eines Expertenworkshops] Stalla, GK, **Athanasoulia, AP**, Führer, D, Frank-Herrmann, P, Oppelt, PG, Hauffa, BP, Dörr, HG Monatsschrift Kinderheilkunde (Internet) A. 2013, vol. 161, n 12, pp. 1180-1186

9. Publications of the habilitation thesis

   Please refer to sections 8.1. and 8.2.

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