Lessons from rare diseases: pathophysiology of stress-related diseases and organization and evaluation of care for patients with Cushing's syndrome

Haalen, F.M. van

CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE

As reaction to undesirable, difficult or challenging circumstances, called stressors, a psychophysiological response is generated to enable an adequate response to these stressors: the stress response.[1-3] Biologically, both the endocrine system as well as the autonomic nervous system play either individually or in close collaboration, a key role in regulating levels of stress.[4, 5] Activation of the hypothalamus-pituitary-adrenal (HPA)-axis leads to secretion of the stress hormone cortisol from the adrenal cortex. Cortisol is the key mediator of the stress response and is required for cognition, behaviour, metabolism, and immunological functioning.[5] Although stress responses are essential for survival and have evolved as adaptive processes, already back in 1956 it was observed that severe, prolonged stress might lead to tissue damage and disease.[6] Persistent (chronic) stress is characterized by prolonged exposure to cortisol, affecting vital organs such as the brain, liver, muscle, cardiovascular system, gastrointestinal system, endocrine system, and immune system.[1]

Cushing's syndrome (CS) is characterized by glucocorticoid excess, most commonly caused by medically prescribed synthetic corticosteroids. Endogenous CS is caused by either adrenocorticotropic hormone (ACTH)-independent adrenal overproduction of cortisol (e.g. an adrenal adenoma, hyperplasia, or carcinoma), or by excess ACTH-secretion from a pituitary adenoma (i.e. Cushing's disease (CD)) or an ectopic ACTH-producing tumor (most often bronchial carcinoids). Endogenous CS is a rare condition, with a reported incidence of only 2-3/million per year, although in selected patient populations such as poorly controlled diabetics and young patients with osteoporosis (particularly men) or hypertension the incidence is higher. The incidence of CD, the most common cause of endogenous CS, is estimated to be 1.2-2.4/million per year.[7, 8] The prolonged tissue exposure to increased levels of glucocorticoids induces changes in body composition (central obesity, osteoporosis, and sarcopenia), an adverse metabolic profile (insulin resistance and diabetes mellitus, hypercoagulability leading to venous and arterial thrombosis, dyslipidemia), hypertension, neuropsychiatric disorders, and also ophthalmological abnormalities may occur.[9-11] Patients with CS may present with typical clinical findings such as facial rounding ('moon face'), plethora, truncal obesity, purple striae, easy bruising, muscle weakness, and a dorsal fat pad, however the clinical manifestation of the syndrome may vary, and the diagnosis can be challenging in mild cases.[12, 13] Associated comorbidities as well as CS itself lead to a decreased quality of life.[14] If left untreated, the prognosis of clinically manifest CS is poor, with an estimated 5-year survival of only 50%. [15] This increased mortality is mainly caused by macrovascular disease (e.g. stroke and myocardial infarction), but also infections, a hypercoagulable state, and poorly controlled diabetes mellitus may play a role.[16]

Resection of primary lesion(s) underlying CS is the treatment modality of first choice, aiming at normalization of cortisol exposure to eliminate the associated symptoms, signs, and comorbidities, reducing mortality and improving prognosis, and to improve quality of life.[17, 18] In case of a pituitary corticotropic adenoma, selective adenomectomy by transsphenoidal resection is the preferred treatment.[19] Second-line therapeutic options include re-operation, medical therapy, radiotherapy, and bilateral adrenalectomy in case of noncurative pituitary surgery.[17] In case of adrenal CS or an ectopic tumor, adrenalectomy, respectively removal of the ACTH-producing tumor, will be performed if possible, or bilateral adrenalectomy will be considered in case of metastatic ectopic

ACTH secretion.[17] Surgical outcomes traditionally focus on biochemical remission, however thereby neglecting life-long complications such as hypocortisolism or hypopituitarism, which also impact quality of life, and are therefore important from a patient perspective.[20-22] Because of the (often prolonged) hypercortisolemic state of patients with CS prior to diagnosis and treatment, this rare condition can be considered a model for the effects of chronic and severe stress and corticosteroid excess on the human body and brain.

An example of a disease in which stress and cortisol are believed to play a role in the pathophysiology is central serous chorioretinopathy (CSC). CSC is a specific chorioretinal eye disease often affecting the macula, in which thickening, hyperpermeability and choroidal congestion damage the retinal pigment epithelium. This process induces serous subretinal fluid accumulation and subsequently detachment of the neuroretina.[23-25] If left untreated, irreversible loss of vision may occur. Although the pathogenesis of CSC is yet to be elucidated, an association of CSC with both psychosocial stress as well as biochemical stress in the form of exogenous corticosteroid use and endogenous hypercortisolism has been reported.[11, 23, 26-28] Therefore, in this thesis CSC is used as a model for stress vulnerability of the eye. Although acute CSC often spontaneously resolves within a few months, in chronic CSC the prolonged presence of subretinal fluid may result in permanent photoreceptor damage, resulting in metamorphopsia and variable deterioration in visual acuity, color vison, and contrast leading to a decreased quality of life.[29, 30] The two most commonly used treatment modalities are high-density subthreshold micropulse laser and photodynamic therapy, of which the latter has been shown to be superior regarding complete resolution of subretinal fluid.[31, 32]

This thesis is consists of two parts. Part one addresses the pathophysiology of stress related diseases, in which the rare stress- and cortisol-related diseases mentioned above serve as a model for stress vulnerability of the retina and the brain. In the second part of this thesis, specific features of the organization of thromboprophylaxis managment, outcome evaluation, and quality of care of patients treated for endogenous Cushing's syndrome are described.

PART ONE

Up to 5% of patients with CS have been reported to have had visual complaints during the active phase of the disease likely due to (one or more episodes of) CSC.[33] CSC has even been described as the presenting symptom of CS.[11] It has been hypothesized that endogenous glucocorticoid excess increases the risk of CSC by altering choroidal coagulation, systemic blood pressure, capillary fragility, and fibroblastic activity.[24, 34] In patients with active endogenous CS, an increased choroidal thickness as a predisposing factor for CSC has been observed, as well as retinal abnormalities.[35, 36] In the study described in **chapter 2**, an ophthalmological screening with multimodal imaging including optical coherence tomography was performed in a series of consecutive patients with active CS without visual complaints, in order to evaluate abnormalities within the CSC spectrum and the potential need for standardized ophthalmological evaluation of all CS patients.

The other way around, in consideration of the suspected relationship between CSC and endogenous hypercortisolism/overactivity of the HPA-axis, it is important to consider whether CSC patients should be screened for CS. To assess the prevalence of CS in patients with chronic CSC and to assess whether chronic CSC is associated with hyperactivity of the HPA-axis, a systematic

screening for the presence of CS in a large cohort of chronic CSC patients was conducted, using a detailed clinical and biochemical evaluation. In addition, perceived stress was evaluated using validated questionnaires. Results of the patients with CSC were compared to the results of gender-matched healthy subjects (**chapter 3**).

The activity of the HPA-axis as a proxy of exposure to stress and cortisol can be measured with a number of different tests. All tests reflect different aspects of exposure to cortisol. To estimate long-term cortisol exposure, concentrations of cortisol in scalp hair can be measured.[37, 38] Increased hair cortisol concentrations have previously been associated with psychopathology, cardiovascular disease, obesity and metabolic syndrome, and the presence of active Cushing's syndrome.[39-41] Also in patients with progressive keratoconus, another ophthalmological disease, elevated levels of hair cortisol have been reported.[42] In order to investigate the suspected relationship between cortisol and chronic CSC, hair cortisol concentrations in a large cohort of chronic CSC patients were evaluated in **chapter 4**. Data of the patients were compared with data of hair cortisol concentrations obtained from the general population of adult control subjects.

In addition to biochemical stress, psychosocial stress and 'type A' behavioural characteristics have traditionally been associated with CSC.[27, 28, 43-45] It has been hypothesized that type A behaviour might induce increased levels of catecholamines and cortisol,[46-48] leading to a predisposition to CSC. In previous studies, however, a characteristic personality profile could not be identified in patients with CSC.[49] Personality also effects coping behaviour.[50] Several studies with a limited number of subjects have reported an association between severe psychosocial stress and the onset of CSC, especially in CSC patients with poor coping mechanisms.[27, 51, 52] Coping behaviour may be subject to self-management training, however, also psychological morbidity such as apathy and irritability may be a potential point of engagement. **Chapter 5** describes a cross-sectional study aiming to assess maladaptive personality traits (i.e. traits related to type A behavioural pattern), apathy and irritability, and coping strategies in patients with chronic CSC, in order to identify potentially modifiable psychosocial factors in support to the current standard treatment.

PART TWO

Mortality in patients with CD is increased compared to the general population.[16, 53] Whether mortality is also increased in patients that have been considered cured after initial therapy because they were in long-term remission of cortisol excess is vital for proper patient management, both from the physician and patient's perspective. The question whether mortality remains increased after initial cure is also important for risk stratification in order to devise strategies for follow-up, including treatment of comorbidities. Furthermore, data on factors predictive of mortality in the cured CD patient population are rare. **Chapter 6** provides a systematic review and meta-analysis aiming at answering this important question.

Patients with remitted CD often report residual psychopathology and persisting impairments in cognitive and executive functioning, [54, 55] and also the reduction in quality of life is reported to persist despite curation.[56] A cognitive function essential to lead a functional life is the cognitive skill of planning. Cognitive planning encompasses neurological processes involved with strategy formulation, coordination, evaluation, and selection of thought sequences, followed by actions

needed to achieve your goal.[57] Reductions of these cognitive competences in remitted CD patients may lead to persisting impaired planning abilities, affecting psychological status, daily functionality, and quality of life. Whether patients with remitted Cushing's disease demonstrate altered performance and brain activity patterns with regard to cognitive planning and executive functioning compared to healthy controls, is studied in **chapter 7** using the Tower of London paradigm, a task requiring planning of intermediate, in many instances counterintuitive, steps to successfully solve a problem.[58]

The association between CS and hypercoagulability has gained growing interest in recent years. An increased risk of venous thromboembolism, both during active hypercortisolism as well as in the postoperative period and even after remission, has been reported by multiple cohort studies, and was recently confirmed in a meta-analysis.[59-61] The underlying mechanisms of, and contributing factors to the hypercoagulable state in CS patients are yet to be unraveled. The hemostatic abnormalities and coagulation profiles previously reported in CS are heterogeneously affected, with different studies reporting diverse hemostatic abnormalities, and no correlation has been found between the severity of hypercortisolism and hemostatic parameters.[59, 60] To date, no prospective studies have been conducted evaluating the effects of prophylactic anticoagulation on the occurrence of venous thromboembolism in patients with CS, and therefore evidence-based guidelines on thromboprophylaxis management in this patient category are lacking.[62] The study described in **chapter 8** aimed to map the current clinical practice for thromboprophylaxis strategies in patients with CS across reference centers of the European Reference Network on Rare Endocrine Conditions, using a survey tool.

In the pursuit of achieving remission, transsphenoidal surgery is the first line treatment in CD. Both remission and complications determine the success of the procedure, as failure to normalize cortisol levels is potentially life threatening,[15] whereas potential complications such as pituitary deficiencies are also associated with comorbidities and reduced quality of life. [20-22, 63] A complicating factor in outcome evaluations of pituitary surgery in CD is the multitude of endocrine evaluations and tests, differences in defining normal test results, and particularly the position of hypocortisolism (the way hypocortisolism is taken into account in outcome evaluations), as well as by what means multiple interventions to achieve the optimal goal are assessed and appreciated. Clinicians will need to deal with discrepant test results in many cases, and ultimately decide on the state of disease. The judgement whether remission or recurrence is present will be based on integrating the (re-)occurrence of clinical signs and symptoms, and the results of subsequent testing. These considerations are well-adapted in clinical decision making, however in registries and outcome studies the definitions of disease state are quite heterogenous and difficult to compare and interpret. Outcome Squares are developed to report multidimensional outcome measures, including both remission and complications, in a standard classification in order to unify different outcome parameters in time, while taking the delicate balance between efficacy and safety into account.[64] **Chapter 9** reports on long-term integrated postoperative follow-up measures in patients with Cushing's disease using the Outcome Squares approach.

REFERENCES

1. Yaribeygi H, Panahi Y, Sahraei H, Johnston TP, Sahebkar A. The Impact of Stress on Body Function: A Review. Excli J. 2017;16:1057-72.
2. Noushad S, Ahmed S, Ansari B, Mustafa UH, Saleem Y, Hazrat H. Physiological biomarkers of chronic stress: A systematic review. Int J Health Sci-Ijh. 2021;15(5):46-59.
3. de Kloet ER, Joels M, Holsboer F. Stress and the brain: from adaptation to disease. Nat Rev Neurosci. 2005;6(6):463-75.
4. Kudielka BM, Wust S. Human models in acute and chronic stress: Assessing determinants of individual hypothalamus-pituitary-adrenal axis activity and reactivity. Stress-the International Journal on the Biology of Stress. 2010;13(1):1-14.
5. Nater UM, Skoluda N, Strahler J. Biomarkers of stress in behavioural medicine. Curr Opin Psychiatr. 2013;26(5):440-5.
6. Selye H. The stress of life. New York: McGraw-Hill Book Company, Inc.; 1956.
7. Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, et al. Incidence and late prognosis of cushing's syndrome: a population-based study. J Clin Endocrinol Metab. 2001;86(1):117-23.
8. Valassi E, Santos A, Yaneva M, Toth M, Strasburger CJ, Chanson P, et al. The European Registry on Cushing's syndrome: 2-year experience. Baseline demographic and clinical characteristics. Eur J Endocrinol. 2011;165(3):383-92.
9. Fernandez-Rodriguez E, Stewart PM, Cooper MS. The pituitary-adrenal axis and body composition. Pituitary. 2009;12(2):105-15.
10. Pereira AM, Tiemensma J, Romijn JA. Neuropsychiatric disorders in Cushing's syndrome. Neuroendocrinology. 2010;92 Suppl 1:65-70.
11. van Dijk EH, Dijkman G, Biermasz NR, van Haalen FM, Pereira AM, Boon CJ. Chronic central serous chorioretinopathy as a presenting symptom of Cushing syndrome. Eur J Ophthalmol. 2016;26(5):442-8.
12. Nieman LK. Cushing's syndrome: update on signs, symptoms and biochemical screening. Eur J Endocrinol. 2015;173(4):M33-8.
13. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. Lancet. 2015;386(9996):913-27.
14. Lindsay JR, Nansel T, Baid S, Gumowski J, Nieman LK. Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission. J Clin Endocrinol Metab. 2006;91(2):447-53.
15. Plotz CM, Knowlton AI, Ragan C. The natural history of Cushing's syndrome. Am J Med. 1952;13(5):597-614.
16. Dekkers OM, Horvath-Puho E, Jorgensen JO, Cannegieter SC, Ehrenstein V, Vandenbroucke JP, et al. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. J Clin Endocrinol Metab. 2013;98(6):2277-84.
17. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(8):2807-31.
18. van Haalen FM, Broersen LH, Jorgensen JO, Pereira AM, Dekkers OM. Management of endocrine disease: Mortality remains increased in Cushing's disease despite biochemical remission: a systematic review and meta-analysis. Eur J Endocrinol. 2015;172(4):R143-9.
19. Hofmann BM, Hlavac M, Martinez R, Buchfelder M, Muller OA, Fahlbusch R. Long-term results after microsurgery for Cushing disease: experience with 426 primary operations over 35 years. J Neurosurg. 2008;108(1):9-18.
20. Crespo I, Santos A, Webb SM. Quality of life in patients with hypopituitarism. Curr Opin Endocrinol Diabetes Obes. 2015;22(4):306-12.
21. Crespo I, Valassi E, Santos A, Webb SM. Health-related quality of life in pituitary diseases. Endocrinol Metab Clin North Am. 2015;44(1):161-70.
22. Webb SM, Santos A, Aulinas A, Resmini E, Martel L, Martinez-Momblan MA, et al. Patient-Centered Outcomes with Pituitary and Parasellar Disease. Neuroendocrinology. 2020;110(9-10):882-8.
23. Liew G, Quin G, Gillies M, Fraser-Bell S. Central serous chorioretinopathy: a review

of epidemiology and pathophysiology. Clin Experiment Ophthalmol. 2013;41(2):201-14.

24. Prunte C, Flammer J. Choroidal capillary and venous congestion in central serous chorioretinopathy. Am J Ophthalmol. 1996;121(1):26-34.

25. Nicholson B, Noble J, Forooghian F, Meyerle C. Central serous chorioretinopathy: update on pathophysiology and treatment. Surv Ophthalmol. 2013;58(2):103-26.

26. Carvalho-Recchia CA, Yannuzzi LA, Negrao S, Spaide RF, Freund KB, Rodriguez-Coleman H, et al. Corticosteroids and central serous chorioretinopathy. Ophthalmology. 2002;109(10):1834-7.

27. Conrad R, Bodeewes I, Schilling G, Geiser F, Imbierowicz K, Liedtke R. [Central serous chorioretinopathy and psychological stress]. Ophthalmologe. 2000;97(8):527-31.

28. Yannuzzi LA. Type A behavior and central serous chorioretinopathy. Trans Am Ophthalmol Soc. 1986;84:799-845.

29. Breukink MB, Dingemans AJ, den Hollander AI, Keunen JE, MacLaren RE, Fauser S, et al. Chronic central serous chorioretinopathy: long-term follow-up and vision-related quality of life. Clin Ophthalmol. 2017;11:39-46.

30. Loo RH, Scott IU, Flynn HW, Jr., Gass JD, Murray TG, Lewis ML, et al. Factors associated with reduced visual acuity during long-term follow-up of patients with idiopathic central serous chorioretinopathy. Retina. 2002;22(1):19-24.

31. van Rijssen TJ, van Dijka EHC, Yzer S, Ohno-Matsui K, Keunen JEE, Schlingemann RO, et al. Central serous chorioretinopathy: Towards an evidence-based treatment guideline. Prog Retin Eye Res. 2019;73.

32. van Dijk EHC, Fauser S, Breukink MB, Blanco-Garavito R, Groenewoud JMM, Keunen JEE, et al. Half-Dose Photodynamic Therapy versus High-Density Subthreshold Micropulse Laser Treatment in Patients with Chronic Central Serous Chorioretinopathy The PLACE Trial. Ophthalmology. 2018;125(10):1547-55.

33. Bouzas EA, Scott MH, Mastorakos G, Chrousos GP, Kaiser-Kupfer MI. Central serous chorioretinopathy in endogenous hypercortisolism. Arch Ophthalmol. 1993;111(9):1229-33.

34. Bouzas EA, Karadimas P, Pournaras CJ. Central serous chorioretinopathy and glucocorticoids. Surv Ophthalmol. 2002;47(5):431-48.

35. Karaca C, Karaca Z, Kahraman N, Sirakaya E, Oner A, Mirza GE. IS THERE A ROLE OF ACTH IN INCREASED CHOROIDAL THICKNESS IN CUSHING SYNDROME? Retina. 2016.

36. Abalem MF, Machado MC, Santos HN, Garcia R, Helal J, Jr., Carricondo PC, et al. Choroidal and Retinal Abnormalities by Optical Coherence Tomography in Endogenous Cushing's Syndrome. Front Endocrinol (Lausanne). 2016;7:154.

37. Gao W, Kirschbaum C, Grass J, Stalder T. LC-MS based analysis of endogenous steroid hormones in human hair. J Steroid Biochem Mol Biol. 2016;162:92-9.

38. Noppe G, de Rijke YB, Dorst K, van den Akker EL, van Rossum EF. LC-MS/MS-based method for long-term steroid profiling in human scalp hair. Clin Endocrinol (Oxf). 2015;83(2):162-6.

39. Manenschijn L, Koper JW, van den Akker EL, de Heide LJ, Geerdink EA, de Jong FH, et al. A novel tool in the diagnosis and follow-up of (cyclic) Cushing's syndrome: measurement of long-term cortisol in scalp hair. J Clin Endocrinol Metab. 2012;97(10):E1836-43.

40. Wester VL, Staufenbiel SM, Veldhorst MA, Visser JA, Manenschijn L, Koper JW, et al. Long-term cortisol levels measured in scalp hair of obese patients. Obesity (Silver Spring). 2014;22(9):1956-8.

41. Wester VL, van Rossum EF. Clinical applications of cortisol measurements in hair. Eur J Endocrinol. 2015;173(4):M1-10.

42. Lenk J, Spoerl E, Stalder T, Schmiedgen S, Herber R, Pillunat LE, et al. Increased Hair Cortisol Concentrations in Patients With Progressive Keratoconus. J Refract Surg. 2017;33(6):383-8.

43. Jenkins CD, Rosenman RH, Friedman M. Development of an objective psychological test for the determination of the coronary-prone behavior pattern in employed men. J Chronic Dis. 1967;20(6):371-9.

44. Baraki H, Feltgen N, Roider J, Hoerauf H, Klatt C. [Central serous chorioretinopathy (CSC)]. Ophthalmologe. 2010;107(5):479-92; quiz 93.

45. Chatziralli I, Kabanarou SA, Parikakis E, Chatzirallis A, Xirou T, Mitropoulos P. Risk Factors for Central Serous Chorioretinopathy: Multivariate Approach in a Case-Control Study. Curr Eye Res. 2017:1-5.

46. Friedman M, St George S, Byers SO, Rosenman RH. Excretion of catecholamines, 17-ketosteroids, 17-hydroxycorticoids and 5-hydroxyindole in men exhibiting a particular behavior pattern (A) associated with high incidence of clinical coronary artery disease. J Clin Invest. 1960;39:758-64.

47. Friedman M, Byers SO, Diamant J, Rosenman RH. Plasma catecholamine response of coronary-prone subjects (type A) to a specific challenge. Metabolism. 1975;24(2):205-10.

48. Williams RB, Jr., Lane JD, Kuhn CM, Melosh W, White AD, Schanberg SM. Type A behavior and elevated physiological and neuroendocrine responses to cognitive tasks. Science. 1982;218(4571):483-5.

49. Bahrke U, Krause A, Walliser U, Bandemer-Greulich U, Goldhahn A. [Retinopathia centralis serosa--stomach ulcer of ophthalmology?]. Psychother Psychosom Med Psychol. 2000;50(12):464-9.

50. Friedman LC, Kalidas M, Elledge R, Chang J, Romero C, Husain I, et al. Optimism, social support and psychosocial functioning among women with breast cancer. Psychooncology. 2006;15(7):595-603.

51. Spahn C, Wiek J, Burger T. [Operationalized psychodynamic diagnostics (OPD) in patients with central serous chorioretinopathy]. Psychother Psychosom Med Psychol. 2004;54(2):52-7.

52. Lahousen T, Painold A, Luxenberger W, Schienle A, Kapfhammer HP, Ille R. Psychological factors associated with acute and chronic central serous chorioretinopathy. Nord J Psychiatry. 2016;70(1):24-30.

53. Bolland MJ, Holdaway IM, Berkeley JE, Lim S, Dransfield WJ, Conaglen JV, et al. Mortality and morbidity in Cushing's syndrome in New Zealand. Clin Endocrinol. 2011;75(4):436-42.

54. Tiemensma J, Biermasz NR, Middelkoop HA, van der Mast RC, Romijn JA, Pereira AM. Increased prevalence of psychopathology and maladaptive personality traits after long-term cure of Cushing's disease. J Clin Endocrinol Metab. 2010;95(10):E129-41.

55. Ragnarsson O, Berglund P, Eder DN, Johannsson G. Long-Term Cognitive Impairments and Attentional Deficits in Patients with Cushing's Disease and Cortisol-Producing Adrenal Adenoma in Remission. J Clin Endocr Metab. 2012;97(9):E1640-E8.

56. van Aken MO, Pereira AM, Biermasz NR, van Thiel SW, Hoftijzer HC, Smit JWA, et al. Quality of life in patients after long-term biochemical cure of Cushing's disease. J Clin Endocr Metab. 2005;90(6):3279-86.

57. Morris RG, Miotto EC, Feigenbaum JD, Bullock P, Polkey CE. Planning ability after frontal and temporal lobe lesions in humans: The effects of selection equivocation and working memory load. Cogn Neuropsychol. 1997;14(7):1007-27.

58. van den Heuvel OA, Groenewegen HJ, Barkhof F, Lazeron RHC, van Dyck R, Veltman DJ. Frontostriatal system in planning complexity: a parametric functional magnetic resonance version of Tower of London task. Neuroimage. 2003;18(2):367-74.

59. van der Pas R, Leebeek FWG, Hofland LJ, de Herder WW, Feelders RA. Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. Clin Endocrinol. 2013;78(4):481-8.

60. Wagner J, Langlois F, Lim DST, McCartney S, Fleseriu M. Hypercoagulability and Risk of Venous Thromboembolic Events in Endogenous Cushing's Syndrome: A Systematic Meta-Analysis. Front Endocrinol. 2019;9.

61. Stuijver DJ, van Zaane B, Feelders RA, Debeij J, Cannegieter SC, Hermus AR, et al. Incidence of venous thromboembolism in patients with Cushing's syndrome: a multicenter cohort study. Journal of Thrombosis and Haemostasis. 2011;9:170-1.

62. Koracevic G, Stojanovic M, Petrovic S, Simic D, Sakac D, Vlajkovic M, et al. Cushing's Syndrome, a Risk Factor for Venous Thromboembolism Is a Candidate for Guidelines. Acta Endocrinol-Buch. 2020;16(2):123-8.

63. Svider PF, Raikundalia MD, Pines MJ, Baredes S, Folbe AJ, Liu JK, et al. Inpatient Complications After Transsphenoidal Surgery in Cushing's Versus Non-Cushing's Disease Patients. Ann Otol Rhinol Laryngol. 2016;125(1):5-11.

64. de Vries F, Lobatto, D.J., Verstegen, M.J.T., Schutte, P.J., Notting, I.C., Kruit, M.C., Ahmed, S.F., Pereira, A.M., van Furth, W.R., Biermasz, N.R. Outcome Squares integrating efficacy and safety, as applied to functioning pituitary adenoma surgery. J Clin Endocrinol Metab. 2021;Mar 6(dgab138).