11. THE ROLE OF GENETIC ASPECTS IN PATHOPHYSIOLOGY OF CUSHING SYNDROME

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Introduction. Cushing's syndrome is considered a rare disease with an incidence of 0.2– 0.5 million population per year, with an average age of 41 years at diagnosis and 1–2 cases per 100,000 population per year. As known, at the base of syndrome stay hypercortisolism, that can be primary, secondary and tertiary. The most frequent cause of syndrome is pituitary adenoma, being 85%. But less encountered and well known is the genetic aspect, being 5% of causes.

Aim of study. To identify the role of genetic factors involved in pathophysiology of Cushing syndrome, as defects in PDE (phosphodiesterase), gene encoding the catalytic subunit of PKA (PRKACA) and ubiquitin-specific peptidase 8 (USP8).

Methods and materials. A synthesis of the literature published between 2020-2023 was performed using databases such as PubMed, Google Scholar, and ScienceDirect. It has been analyzed and 30 relevant articles and literature reviews published in the last decade, were reviewed to compile a comprehensive approach in pathophysiology of Cushing syndrome.

Results. As known the secretion of cortisol is dependent on the functioning of the hypothalamic-pituitary-adrenal axis, mediated by the hormones such as CRH and ACTH, feedback mechanism and on the different regulatory enzymes. The ACTH acts on the MCR2 receptors on the adrenal gland, which interact with specific associated proteins, activates adenylate cyclase (AC) and form cAMP that releases the C subunit from its inactivating regulatory form of PKA (PRKACA), thus activating PKA that phosphorylates different intracellular targets genes and transcription factor, responsible for synthesis of cortisol. Genetic defects of PRKAR1A gene lead to increased free catalytic subunits and protein kinase A activity. The mechanism that counteracts the action of PKA is the specific enzyme phosphodiesterase (PDE) which is responsible for the degradation of the intracellular cAMP, such decreasing activity of PKA. Genetic defects of PDE lead to permanent activation of PKA, leading to oversecretion of cortisol. New gene variant identified in the pathogenesis of Cushing's syndrome, as ubiquitin-specific peptidase 8 (USP8) gene, is responsible for recycling to the plasma membrane of epidermal growth factor receptor (EGFR) founded on pituitary corticotroph cells. The mutation of USP8 results in increased deubiquitination of EGFR that activates a mitogen activated protein kinase (MAPK)-dependent pathway which stimulates the expression of the ACTH secretion and in turn cortisol secretion.

Conclusion. Studying the literature, it has been found that a big role in pathogenesis of Cushing syndrome also has genetic factors, such as defects in PRKAR1A gene, defects in PDE gene expression, and more new research identifies another cause as mutation in USP8 gene. All of these gene defects are responsible for the development of hypercortisolism ACTH dependent and independent and are promising targets in a therapeutic perspective for Cushing’s syndrome patients.