LUMEN ET VIRTUS
ISSN: 2177-2789

PATHOPHYSIOLOGY AND MANAGEMENT OF CUSHING'S SYNDROME: A SYSTEMATIC REVIEW OF CURRENT AND FUTURE PERSPECTIVES

https://doi.org/10.56238/levv15n41-078

Submitted on: 09/22/2024 **Publication date:** 10/22/2024

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ABSTRACT

Objective: The general objective of this study is to analyze the scientific production on Cushing's Syndrome (CS), seeking to identify the main clinical manifestations, complications and the impact on the quality of life of patients. Methodology: Searches were performed in the PubMed Central (PMC) databases, using three descriptors in combination with the Boolean term "AND": Cushing Syndrome, Clinical Manifestations, Complications, and Quality of Life. A total of 161 articles were found, which were subsequently submitted to the selection criteria. A total of 22 studies were selected to compose this systematic review, of which 12 were used. Results: Cushing's Syndrome is a condition characterized by hypercortisolism, which results in a wide range of clinical manifestations. Among the complications associated with CS are visceral obesity, arterial hypertension, diabetes mellitus, dyslipidemia, osteoporosis, and myopathy. In addition, CS has a significant impact on patients' mental health, including depression, anxiety, and cognitive impairment. Therapeutic approaches range from transsphenoidal surgery, radiotherapy, to targeted drug treatments to normalize cortisol levels and address comorbidities. Conclusion: CS is associated with several comorbidities that affect multiple body systems, resulting in a

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significant impact on the quality of life of patients. Early diagnosis and multidisciplinary treatment are essential to improve clinical outcomes and quality of life in these patients.

Keywords: Cushing's syndrome. Complications. Clinical manifestations. Quality of life.

INTRODUCTION

Cushing's syndrome (CS) is a complex and challenging condition resulting from prolonged exposure to high endogenous cortisol levels. Cushing's disease (CD), caused by adrenocorticotropic hormone (ACTH)-producing pituitary tumors, accounts for about 70% of cases. The remaining 30% is attributed to primary adrenal hyperfunction, also known as ACTH-independent SC (THEODOROPOULOU; REINCKE, 2022). The endogenous form is often caused by Cushing's disease (CD), which is an adrenocorticotropic-secreting pituitary adenoma (ACTH), overstimulating the adrenal glands to produce cortisol. Other causes of endogenous CS include ectopic production of ACTH by neuroendocrine tumors or autonomic production of cortisol by adrenal glands (GROSELJ; SYLKONJA; BATTELINO, 2023) (THEODOROPOULOU; REINCKE, 2022). The exogenous form, on the other hand, is usually due to long-term use of glucocorticoids prescribed to treat various inflammatory and autoimmune diseases (GROSELJ; SYLKONJA; BATTELINO, 2023).

Endogenous CS has an annual incidence of 0.7 to 2.4 cases per million in the general population, while in children, CD accounts for about 75-80% of endogenous CS cases. In pediatrics, CD manifests mainly with signs of hypercortisolism, such as facial changes, weight gain, growth failure, virilization, disturbed puberty, and psychological disorders. Microadenomas are prevalent in children, while macroadenomas are less common. In addition, the gender distribution has a male predominance before puberty and a balanced incidence during puberty (FERRIGNO et al., 2021).

Hypercortisolism is characterized by marked clinical features, including a full moon face, facial plethora, red striae, and supraclavicular and dorsal fat deposits. In addition, it is associated with metabolic complications such as visceral obesity, hypertension, diabetes, dyslipidemia, and osteoporosis, as well as adverse impacts on the brain, such as damage to the hippocampus and memory impairment (THEODOROPOULOU; REINCKE, 2022) (PARAGLIOLA et al., 2021). The clinical manifestations of CS are diverse, affecting multiple body systems. Patients with CS often have central fat accumulation, leading to obesity, hypertension, glucose intolerance, stretch marks and skin atrophy, fungal infections, osteopenia, hypogonadism, and depression (GROSELJ; SYLKONJA; BATTELINO, 2023; DEKKERS et al., 2022; LESZCZYŃSKA et al., 2023). In children, excessive weight gain and failure to thrive are common, in addition to signs such as early or late puberty and hyperandrogenism in girls (GROSELJ; SYLKONJA; BATTELINO, 2023). These symptoms vary in intensity and combine to significantly affect patients' quality of life (GROSELJ; SYLKONJA; BATTELINO, 2023).

In the context of musculoskeletal complications, CS is notorious for causing osteopenia, osteoporosis, and myopathy. Although endogenous hypercortisolemia is a rare condition, chronic administration of glucocorticoids (GCs) for other conditions makes exposure to excess GCs a common occurrence. Understanding the pathophysiology of these effects is crucial to develop appropriate preventive and therapeutic strategies (LESZCZYŃSKA et al., 2023). Epidemiologically, endogenous CS is rare, with an estimated incidence of 2 to 5 cases per million people per year (GROSELJ; SYLKONJA; BATTELINO, 2023). This condition is more common in young women and middle-aged adults. In children, CD is extremely rare, accounting for about 10% of all cases, with a predominance in girls after puberty (GROSELJ; SYLKONJA; BATTELINO, 2023).

RESULTS:

Table 1- RESULT OF THE SYSTEMATIC REVIEW

Author	Major Contributions
Fleseriu et al. (2021)	They detailed the variability and insidious presentation of CS symptoms, highlighting the importance of nocturnal salivary cortisol (SCNL) and the dexamethasone suppression test to assess cortisol levels and differentiate CS from pseudo-CS.
Theodoropoulou & Reincke (2022)	They examined the pathophysiology of CS, including Cushing's disease caused by ACTH-secreting pituitary adenomas, metabolic and neurological complications such as hippocampal damage and memory impairment, and prevalence among different demographic groups.
Ferrigno et al. (2021)	They analyzed the clinical manifestations in children with Cushing's disease (CD), including signs of hypercortisolism, such as weight gain, disturbed puberty, virilization, and challenges in pediatric diagnosis and treatment.
Groselj, Sikonja & Battelino (2023)	They presented the incidence and prevalence of CS in children, analyzing gender distribution and specific complications, such as early or delayed puberty, hyperandrogenism in girls, and impacts on quality of life and growth.
Paragliola et al. (2021)	They discussed the effects of hypercortisolism on thyroid function, including reduced HRT expression and increased somatostatin, leading to changes in TSH and FT4 levels, and how these impacts contribute to hypertension and cardiovascular disease.
Dekkers et al. (2022)	They highlighted the diversity of clinical manifestations of CS, including central fat accumulation, hypertension, glucose intolerance, and the importance of differentiating CS from other conditions with similar symptoms.
Leszczyńska et al. (2023)	They examined the effects of glucocorticoids on the musculoskeletal system, detailing how hypercortisolism induces osteopenia, osteoporosis, myopathy, and treatment strategies such as calcium and vitamin D supplementation and the use of bisphosphonates.

Author	Major Contributions
Takayasu, Kageyama & Daimon (2023)	They investigated genetic mutations, such as USP8 and BRAF, their contribution to ACTH overproduction, glucocorticoid resistance, and the development of new targeted therapies, such as HSP90 and EGFR inhibitors.
Webb & Valassi (2022)	They analyzed the pathophysiology of corticotrophic tumors, highlighting the somatic mutations in USP8 and TP53, the response to different therapies, and how these mutations influence the clinical presentation and treatment.
Feingold, Brinton & Grunfeld (2017)	They studied the effects of glucocorticoids on the cardiovascular system, including sodium and water retention that leads to hypertension, increased cholesterol and triglyceride levels, and the increased risk of cardiovascular disease.
Lin, Hanna & Ishak (2020)	They investigated the impact of hypercortisolism on neurocognitive and emotional functions, such as hippocampal atrophy, memory deficits, and executive functions, and the importance of continuous psychological support to improve patients' quality of life.
Pivonello et al. (2020)	They examined the efficacy of combination therapies in the treatment of CS, showing significant improvements in urinary cortisol excretion, control of comorbidities such as hypertension and diabetes mellitus, and the benefits of combining different classes of drugs to increase efficacy and reduce adverse effects.

Source: Table created by the author

DISCUSSION

Diagnosing CS can be challenging due to the variability and insidious presentation of symptoms (FLESERIU et al., 2021). Essential diagnostic tests include the measurement of nocturnal salivary cortisol (LNSC), which assesses the circadian rhythm of cortisol (FLESERIU et al., 2021). In patients with CS, this rhythm is altered, with elevated cortisol levels at night (FLESERIU et al., 2021). Dexamethasone suppression testing is another important tool; in this test, it is verified that cortisol is adequately suppressed after the administration of dexamethasone, with elevated levels indicating CS. 24-hour urine free cortisol (CFU) is used to measure cortisol excretion in the urine, and is useful for assessing total cortisol production. In addition, certain conditions, such as psychiatric disorders and alcohol use, can cause non-neoplastic hypercortisolism, known as pseudo-SC.

Differentiating between pseudo-SC and true SC can be done through specific tests such as LDDT-CRH and desmopressin stimulation (FLESERIU et al., 2021).

Imaging techniques such as magnetic resonance imaging (MRI) are crucial for detecting ACTH-secreting pituitary adenomas. However, due to the small size of many adenomas, only approximately 50% of microadenomas are detected with standard MRI. Technical improvements and alternatives such as 18F-FDG PET/CT can improve the detection of small adenomas (FLESERIU et al., 2021).

With regard to the genetics of Cushing's disease, the pathogenesis of CD involves ACTH-secreting adenomas, which are mostly monoclonal and sporadic. Recent studies have identified genetic mutations that contribute to the etiology of CD. Mutations in the USP8 gene have been found in 31-63% of pediatric corticotrophic adenomas, affecting epidermal growth factor receptor (EGFR) stability and resulting in ACTH overproduction. Other mutations include USP48 and BRAF, which increase the activity of the POMC gene promoter, leading to overproduction of ACTH. The relationship with mutations in the MEN1 gene has also been observed, especially in multiple endocrine neoplasia type 1 (MEN1) syndromes, although rare in pediatrics (FERRIGNO et al., 2021).

Somatic mutations in the USP8 gene have been identified in 24-60% of corticotrophic tumors, frequently observed in female patients and presenting as smaller tumors with strong POMC expression and ACTH production. These mutations increase enzyme activity, resulting in excessive deubiquitination of the epidermal growth factor receptor (EGFR), disrupting its degradation and increasing its recycling. EGFR overexpression is associated with cell proliferation and ACTH production in corticotrophic tumors. EGFR inhibitors such as gefitinib have been shown to attenuate POMC expression and ACTH secretion, suggesting that EGFR-targeted therapy may be effective (TAKAYASU; KAGEYAMA; DAIMON, 2023).

Overexpression of cyclin E and low levels of p27 are seen in Cushing's disease. "Cyclin E" is correlated with the loss of p27 in human corticotrophic tumors. Cyclin E inhibitors, such as R-roscovitin, have been shown to inhibit ACTH secretion in primary cell cultures from human tumors. Studies have shown that the combination of cyclin E overexpression and p27 knockout increases the proliferation and size of pituitary tumors, consequently acting as a risk factor for the syndrome (TAKAYASU; KAGEYAMA; DAIMON, 2023). ACTH-producing corticotropic tumors require higher doses of glucocorticoids to inhibit ACTH secretion. Resistance is caused by overexpression of HSP90, which restricts the release of mature glucocorticoid (GR) receptors. HSP90 inhibitors, such as silibinin, can restore sensitivity to glucocorticoids. BRG1 and HDAC2 are required for the recruitment of

glucocorticoid receptors, and the loss of these proteins is associated with partial resistance to glucocorticoids (TAKAYASU; KAGEYAMA; DAIMON, 2023).

Familial genetic syndromes, such as familial isolated pituitary adenoma, multiple endocrine neoplasia, and McCune-Albright syndrome, are rarely found in Cushing's disease. Mutations in the BRAF gene (p.V600E) increase POMC transcription and ACTH secretion by activating the MAPK pathway. These mutations are rare in corticotrophic tumors, but when present, they play a significant role in the pathogenesis of the disease and its phenotypic manifestation (TAKAYASU; KAGEYAMA; DAIMON, 2023).

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In a genetic context, most corticotrophic pituitary tumors that cause Cushing's disease develop sporadically, and only a few cases involve multiple inherited endocrine syndromes. These include familial isolated pituitary tumour (FIPA; AIP), multiple endocrine neoplasia type 1 (MEN1) and type 4 (CDKN1B), Carney complex (PRKAR1A) and DICER 1 syndrome. Corticotrophic tumors account for about 5% of all pituitary tumors in FIPAs. To date, no germline mutations in GNAS or PRKAR1A have been reported in CD. DICER1 germline mutations have been described in pituitary blastoma, a rare cause of infantile-onset CD (WEBB; VALASSI, 2022).

Approximately half of functional corticotrophic tumors, including pediatric and Nelson Syndrome cases, have mutations in the USP8 gene, resulting in greater ACTH synthesis (TAKAYASU; KAGEYAMA; DAIMON, 2023). Somatic mutations in the NR3C1 gene, which encodes the glucocorticoid receptor, have been identified in up to 10% of corticotrophic tumors, although they were initially considered rare (TAKAYASU; KAGEYAMA; DAIMON, 2023). Increasing reports of somatic mutations in the TP53 and ATXR genes are linked to aggressive corticotrophic tumors and carcinomas (TAKAYASU; KAGEYAMA; DAIMON,

2023). Mutations in TP53 have been found in up to 35% of functional wild-type macroadenomas USP8 (TAKAYASU; KAGEYAMA; DAIMON, 2023).

The pathogenic mechanisms of corticotrophic tumors remain largely unknown. One of the important recent advances is the detection of mutations of the ubiquitin-specific peptidase 8 (USP8) gene in approximately 23–60% of functional corticotrophic tumors. Somatic mutations are specific for corticotrophic tumors and lead to increased EGFR expression and activation of proopiomelanocortin (POMC) gene transcription. The phenotype of mutations typical of USP8 represents a Cushing's disease with small tumors in middle-aged women. The mutation is infrequent in Crooke cell tumor, a histological subtype of corticotrophic tumor, which often shows aggressive clinical behavior. Corticotrophic tumors with USP8 mutations have significantly higher expression levels of SSTR5 and MGMT than those with the wild-type. Consequently, patients with USP8 mutant tumors may have better surgical outcomes and may respond more favorably to SSTR5-targeted somatostatin analogues than patients with wild-type tumors (WEBB; VALASSI, 2022). Pediatric patients with USP8 mutations had more severe overall disease, with higher rates of primary surgical resection failure and an increased risk of recurrence (WEBB; VALASSI, 2022).

CD has a significant impact on the quality of life of pediatric patients. Mood swings, depression, and emotional lability are common due to prolonged hypercortisolism. Brain atrophy seen on imaging tends to improve after remission, but deficits in cognitive function may persist. Continuous psychological support is essential to help with recovery and improve long-term quality of life (FERRIGNO et al., 2021).

Approximately 80–90% of corticotrophic pituitary tumors that cause CD are microtumors, most of which are very small tumors contained in the sella turcica. Thus, CD patients showing signs of sellar mass effect, such as visual disturbances, which are uncommon. However, these patients have various symptoms of hypercortisolism and comorbidities. In addition, clinical presentations can be highly variable and diagnosis tends to be delayed by about 2–4 years. In general, clinical features are less apparent in men than in women (WEBB; VALASSI, 2022).

Glucocorticoids have a profound impact on the hypothalamic-pituitary-thyroid (HPT) axis, which is crucial for the regulation of thyroid function. The secretion of thyroid-stimulating hormone (TSH) by the pituitary gland is influenced by the release of thyrotropin-releasing hormone (TRH) from the hypothalamus, creating a negative feedback system that maintains homeostasis. Chronic hypercortisolism may reduce TRH expression in the paraventricular nucleus (PVN) of the hypothalamus and increase the release of

somatostatin (TSS), which inhibits TSH release. In addition, hypercortisolism affects the peripheral deiodination of thyroid hormones, leading to a decrease in the T3:T4 ratio (PARAGLIOLA et al., 2021).

Clinical studies have shown that hypercortisolism reduces TSH secretion and alters the pulse rate of TSH in patients with CS. In cases of pituitary and adrenal CS, TSH and FT4 levels are often reduced during the active phase of the disease. After surgical cure, a gradual recovery of thyroid function is observed, with recovery time inversely related to the severity of previous hypercortisolism. This phenomenon has been confirmed by several studies, which have shown a normalization of TSH and thyroid hormone levels after resolution of hypercortisolism (PARAGLIOLA et al., 2021).

Remission of hypercortisolism can trigger or exacerbate autoimmune thyroid diseases such as De Quervain's thyroiditis (DQT) and TSH inappropriate secretion syndrome (SITS). Patients with CS have a high prevalence of underlying autoimmune thyroid disease, which may be masked by glucocorticoid excess. The sudden reduction in cortisol levels after successful treatment can trigger an autoimmune response, leading to the development of autoimmune hyperthyroidism and other inflammatory conditions. Studies demonstrate a significant increase in antithyroid antibody titers after resolution of hypercortisolism, suggesting a direct link between decreased immune tolerance and steroid excess (PARAGLIOLA et al., 2021).

Excessive cortisol production affects diverse body systems in complex and interconnected ways. With regard to lipid metabolism, CS is associated with increased levels of total cholesterol and LDL-C. Cortisol promotes lipogenesis by increasing fat production and storage in the liver and adipose tissue, resulting in elevated levels of total cholesterol and LDL-C. Triglycerides also tend to be elevated, increasing cardiovascular risk. In contrast, glucocorticoid administration often increases levels of HDL-C, the "good cholesterol," although this effect is modest. Cortisol has a profound impact on carbohydrate, protein, and lipid metabolism. It increases gluconeogenesis, raising blood glucose levels and can lead to hyperglycemia and insulin resistance, resulting in diabetes mellitus (FEINGOLD; BRINTON; GRUNFELD, 2017).

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paraventricular nucleus (PVN) of the hypothalamus and increase somatostatin (TSS) release,

In addition, cortisol promotes proteolysis, resulting in the breakdown of muscle proteins and leading to muscle weakness and atrophy. This protein degradation is particularly pronounced in the upper and lower limbs, making it difficult to perform daily activities and compromising the quality of life of patients (FEINGOLD; BRINTON; GRUNFELD, 2017). Glucocorticosteroid-induced myopathy (GIM) is another significant musculoskeletal complication associated with CS. The pathophysiology of GIM involves both increased protein catabolism and decreased protein synthesis. GCs activate catabolic systems, such as the ubiquitin proteasome and lysosomal systems, through the overexpression of atrogene genes such as FOXO-1 and atrogine-1. In addition, GCs inhibit the mTOR signaling pathway, responsible for protein synthesis, and reduce the production of IGF-1, which is essential for maintaining muscle mass (LESZCZYŃSKA et al., 2023).

The effect of cortisol on bones is equally concerning. This hormone promotes bone resorption, resulting in osteopenia and osteoporosis, which significantly increases the risk of fractures. Patients with CS often have vertebral fractures due to bone fragility, which contributes to chronic pain and physical disability (FEINGOLD; BRINTON; GRUNFELD, 2017). Chronic exposure to GCs, regardless of whether it is endogenous or exogenous, results in a significant deterioration of bone health. The pathophysiology of the effects of GCs on bone reveals that these hormones disrupt bone formation processes through inhibition of the Wnt/β-catenin signaling pathway, induction of nuclear factors of the CCAAT/enhancer-binding protein (C/EBP) family and peroxisome proliferator-activated receptor (PPAR-γ) type 2, in addition to repression of bone morphogenetic protein (BMP-2). This inhibition reduces the differentiation and function of osteoblasts, cells responsible for bone formation, and promotes the apoptosis of these cells. As a result, bone loss is disproportionate to bone mass, leading to an increased risk of fractures, even in patients with normal or low-normal bone mineral density (BMD) (LESZCZYŃSKA et al., 2023).

GCs also affect the balance between nuclear factor-κB receptor activator ligand (RANKL) and osteoprotegerin (OPG), promoting an initial increase in bone resorption by osteoclasts. In addition to the direct effects on bones, GCs inhibit the secretion of gonadal hormones and the IGF-1 (GH-IGF-1) axis, both of which are essential for the formation and maintenance of bone mass. Decreased intestinal calcium absorption and increased renal calcium excretion are other indirect mechanisms by which GCs contribute to osteoporosis. Thus, the prevention and treatment of GC-induced osteoporosis (GIO) involves calcium and

vitamin D supplementation, lifestyle modifications, and, in some cases, the administration of antiosteoporotic drugs such as bisphosphonates (LESZCZYŃSKA et al., 2023).

The treatment of musculoskeletal complications of CS involves both pharmacological and behavioral approaches. Calcium and vitamin D supplementation, along with bisphosphonate administration, is widely recommended. In the case of GIM, adequate protein intake and physical therapy are key. In addition, growth factors such as IGF-1 and ghrelin have shown therapeutic potential in animal models and may be promising targets for the treatment of GC-induced myopathy in humans. Androgen administration may also help prevent the reduction in muscle strength associated with excess GCs (LESZCZYŃSKA et al., 2023). Patients with CS often have Metabolic Syndrome. The main components include visceral obesity, symptoms of protein loss, hyperglycemia, and dyslipidemia. Multiple metabolic morbidities persist at least partially, even after CD remission

Centripetal (visceral) fat deposition is the most common symptom and often the initial symptom in patients with CD. Abnormal fat distribution tends to develop on the face (full moon face) and dorsocervical (buffalo hump) and supraclavicular fat pads. This specific fat distribution usually resolves after cortisol levels normalize and is an important finding in distinguishing CD from simple obesity. Weight gain is a common, but not definitive, feature in patients with CD (WEBB; VALASSI, 2022).

Other important clinical findings of CD that are absent in simple obesity include thinning of the skin, wide purple striae, and proximal muscle atrophy, due to the protein-wasting effect of cortisol. The skin becomes fragile to minor traumas, causing bruises, ulcerations and frequent infections (FEINGOLD; BRINTON; GRUNFELD, 2017; WEBB; VALASSI, 2022). The impact of this condition of glucocorticoid exposure on patients' mental and physical health is significant, with a wide range of psychiatric and neurocognitive manifestations, as well as debilitating physical symptoms (LIN; HANNA; ISHAK, 2020). The prevalence of psychiatric symptoms, including depression, anxiety, mania, psychosis, and panic disorder, is a notable feature among patients with CS. Studies indicate that depression is the most common psychiatric condition, affecting up to 90% of patients. This is compounded by hypercortisolemia, which dysregulates cortisol in the brain, leading to decreased activation in the emotional processing centers and difficulties in categorizing facial expressions (LIN; HANNA; ISHAK, 2020).

This hormonal dysregulation causes hippocampal atrophy and cognitive impairment, negatively impacting patients' memory and concentration. The treatment of CS aims to normalize cortisol levels, and different therapeutic approaches have been explored. Medications such as metyrapone, ketoconazole, and mifepristone are used to reduce

glucocorticoid synthesis, while antidepressants and cognitive-behavioral therapies help relieve psychiatric symptoms. Despite biochemical remission, many patients continue to suffer from depression, anxiety, and other neurocognitive disorders due to persistent changes in the brain caused by prolonged exposure to cortisol (LIN; HANNA; ISHAK, 2020).

The pathophysiology of CS involves complex interactions between the hypothalamic-pituitary-adrenal (HPA) axis and the central nervous system (LIN; HANNA; ISHAK, 2020). Chronic hypercortisolism results in neuroanatomical and neurofunctional changes, especially in the hippocampus and amygdala, areas critical for emotional and cognitive processing. Prolonged exposure to elevated cortisol levels leads to loss of brain volume and hippocampal atrophy, contributing to deficits in memory and executive functions. The quality of life of patients with CS is significantly impaired. Studies show that these patients have a negative perception of body image, a higher prevalence of depression and anxiety, and poorer physical health and social adjustment compared to healthy individuals and those with other pituitary diseases. Even after CS is cured, many patients continue to face emotional and cognitive challenges, highlighting the need for ongoing follow-up and comprehensive therapeutic strategies to improve overall well-being (LIN; HANNA; ISHAK, 2020).

In addition, CS can lead to permanent changes in the brain, even after cortisol levels normalize. Patients in remission may continue to experience psychiatric and neurocognitive symptoms due to irreversible damage to the hippocampus. Full recovery of premorbid functioning and quality of life is rare, and many patients continue to experience impairments in various areas of life (LIN; HANNA; ISHAK, 2020). Early normalization of cortisol levels is crucial to minimize psychiatric and neurocognitive effects (LIN; HANNA; ISHAK, 2020).

Easy bruising and purplish stretch marks, especially in the abdomen (FEINGOLD; BRINTON; GRUNFELD, 2017). These stretch marks are the result of the rupture of collagen fibers in the skin, reflecting the fragility of the connective tissue (FEINGOLD; BRINTON; GRUNFELD, 2017). In addition, hypertension is a common complication in CS, resulting from the effect of cortisol on the cardiovascular system (FEINGOLD; BRINTON; GRUNFELD, 2017). Cortisol increases sodium and water retention in the kidneys, leading to the expansion of blood volume and, consequently, high blood pressure (FEINGOLD; BRINTON; GRUNFELD, 2017). This hypertension, along with elevated levels of total cholesterol, LDL-C, and triglycerides, significantly increases the risk of cardiovascular disease, including atherosclerosis, heart attacks, and strokes (FEINGOLD; BRINTON; GRUNFELD, 2017).

The diagnosis of CD involves multiple steps to confirm hypercortisolism and identify its dependence on ACTH. Initially, it is crucial to exclude exogenous administration of corticosteroids. Then, biochemical tests such as 24-hour urinary free cortisol (CFU), salivary/nocturnal serum cortisol, and the dexamethasone suppression test are performed. The UFC should be corrected by body surface area for accuracy. Measurement of plasma ACTH levels helps differentiate the causes of hypercortisolism, and CRH stimulation testing can distinguish CD from other etiologies. Pituitary magnetic resonance imaging (MRI) is essential to visualize corticotrophic adenomas. However, the low prediction rate requires complementary techniques such as bilateral inferior petrosal sinus sampling (BIPSS), which demonstrates the lateralization of ACTH secretion and helps in localizing the adenoma before surgery (FERRIGNO et al., 2021).

The first-line treatment for CD is transsphenoidal surgery (TSS), which aims at selective removal of the corticotrophic adenoma. This technique is challenging in children due to the specific anatomical characteristics of the sellar region, requiring experienced surgeons. Endoscopic TSS is a less invasive approach and is increasingly adopted. Remission is achieved in 70-100% of cases, depending on the surgeon's skill and the location of the adenoma. When TSS is not curative, other options include pituitary radiation therapy (RT), which suppresses ACTH secretion and is effective in reducing hypercortisolism over months. Medical therapy with ketoconazole, metyrapone, or mitotane may be used to suppress adrenal steroidogenesis, especially pending the efficacy of RT. Bilateral adrenalectomy is a last-resort option to quickly eliminate hypercortisolism, but it requires lifelong replacement of glucocorticoids and mineralocorticoids (FERRIGNO et al., 2021).

The recurrence of CD is a long-term concern. Studies show that the recurrence rate ranges between 10-30%, usually occurring years after the initial remission. Continuous monitoring of cortisol and ACTH levels is essential to detect relapses early. Recovery of the hypothalamic-pituitary-adrenal axis can take several months, during which glucocorticoid replacement is necessary (FERRIGNO et al., 2021).

Surgical excision of the tumor is the primary treatment, but stereotactic radiation therapy such as Gamma Knife or Cyberknife is an option when there are residual or recurrent tumors. Medical therapies include pasireotide, a somatostatin analogue, and cabergoline, a dopamine receptor agonist. Both show good results in reducing ACTH and cortisol levels, but require careful monitoring due to possible adverse effects such as hyperglycemia (TAKAYASU; KAGEYAMA; DAIMON, 2023).

Combination therapy has emerged as a promising approach in the treatment of CS, especially in patients with CD who do not respond adequately to monotherapy. The combination of different classes of drugs can improve efficacy by attacking multiple pathophysiological pathways of the disease. In addition, the use of lower doses of drugs in a combination may reduce the incidence of adverse events associated with high doses of monotherapies (PIVONELLO et al., 2020).

Several studies have demonstrated the efficacy of combined therapies in patients with CS and CD. For example, the combination of ketoconazole, metyrapone, and mitotane showed rapid normalization of urinary cortisol excretion (UC) in 63.6% of patients with severe CS, with significant improvement in clinical status. In another study, the combination of pasireotide, cabergoline, and ketoconazole resulted in UC normalization in 88.2% of CD patients, with improvements in waist circumference, blood pressure, and quality of life (PIVONELLO et al., 2020).

The use of combination therapies has also shown substantial clinical benefits in terms of controlling hypercortisolism-related comorbidities, such as hypertension and diabetes mellitus. The combination of cabergoline and ketoconazole demonstrated UC normalization in 66.7% to 83.3% of patients with persistent CD after surgery, with improvement in glycated hemoglobin (HbA1c) levels, body weight, and need for antihypertensive medications. The association of glucocorticoid receptor (GR) antagonists, such as mifepristone, with agents targeting the pituitary or adrenal gland, may provide more effective control of comorbidities, while preventing tumor growth or even promoting tumor reduction (PIVONELLO et al., 2020).

Medical therapy with ketoconazole, metyrapone, or mitotane may be used to suppress adrenal steroidogenesis, especially pending the efficacy of RT. Bilateral adrenalectomy is a last-resort option to quickly eliminate hypercortisolism, but it requires lifelong replacement of glucocorticoids and mineralocorticoids (FERRIGNO et al., 2021).

Promising new treatments include USP8, EGFR, and HSP90 inhibitors, which have been shown to reduce ACTH production and cell proliferation in AtT-20 tumor cells. Histone deacetylase (HDAC) inhibitors, such as romidepsin, have also been shown to block cell proliferation and ACTH synthesis. Immunotherapy with immune checkpoint inhibitors (ICIs) such as ipilimumab and nivolumab has been shown to decrease ACTH levels and metastases in aggressive corticotrophic carcinomas (TAKAYASU; KAGEYAMA; DAIMON, 2023). TP53 and ATXR genes are linked to aggressive corticotrophic tumors and carcinomas (THEODOROPOULOU; REINCKE, 2022). Mutations in TP53 have been found

in up to 35% of functional wild-type macroadenomas USP8 (THEODOROPOULOU; REINCKE, 2022).

CONCLUSION

Cushing's Syndrome is a complex condition that profoundly impacts multiple body systems, resulting in a wide range of clinical manifestations and complications. Early and accurate diagnosis is essential to mitigate adverse effects and improve patients' quality of life. Developments in the understanding of pathogenesis, especially genetic discoveries, have enabled the development of more effective and targeted therapeutic approaches.

Despite advances in transsphenoidal surgery and drug therapy, the recurrence of the disease and the lingering effects on patients' physical and mental well-being highlight the need for continuous and integrated treatment strategies. Continued research into new treatments and therapeutic combinations is crucial to offer hope and better prognosis for those affected by the syndrome.

Finally, the importance of multidisciplinary care, which includes psychological support and educational strategies, is imperative to address all dimensions of the impact of CS. By expanding knowledge about the disease and its multiple facets, it is possible to promote a more holistic and effective approach to the management of Cushing's Syndrome, leading to a significant improvement in the quality of life of patients.

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