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Quality of Life in Cushing's disease: A long term issue?☆

La qualité de vie dans la maladie de Cushing : une affaire à long terme ?

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Abstract

The purpose of this review is to describe how quality of life (QoL) is impaired in patients with hypercortisolism due to Cushing's syndrome of any aetiology, including pituitary-dependent Cushing's disease. It is worse in active disease, but improvement after successful therapy is often incomplete, due to persistent physical and psychological co-morbidities, even years after endocrine "cure". Physical symptoms like extreme fatigability, central obesity with limb atrophy, hypertension, fractures, and different skin abnormalities severely impair the affected patients' everyday life. Psychological and cognitive problems like bad memory, difficulties to concentrate and emotional distress, often associated with anxiety and depression, make it difficult for many patients to overcome the aftermath of treated Cushing's syndrome. Recent studies have shown diffuse structural abnormalities in the central nervous system during active hypercortisolism, thought to be related to the wide distribution of glucocorticoid receptors throughout the brain. Even though they improve after treatment, normalization is often not complete. Shortening the exposure to active Cushing's syndrome by reducing the often long delay to diagnosis and promptly receiving effective treatment is highly desirable, together with preparing the patient for the difficult periods, especially after surgery. In this way they are prepared for the impairments they perceive in every day life, and live with the hope of later improvement, which can be therapeutic in many instances.

Keywords: Cushing's syndrome; Quality-of-life impairment; Persistent co-morbidities; Anxiety; Depression; Coping

Résumé

L'objectif de cette revue est de décrire l'altération de la qualité de la vie en cas d'hypercorticisme induit par la maladie de Cushing, toutes étiologies confondues, y compris le Cushing hypophysaire. Cette altération est maximale en phase active de la maladie, mais l'amélioration apportée par le traitement n'est souvent que partielle, à cause des comorbidités physiques et psychologiques résiduelles, même des années après la « guérison » endocrinologique. Des symptômes physiques tels qu'une fatigabilité extrême, uneobésité centrale avec atrophie musculaire des membres, une hypertension artérielle, des fractures et diverses anomalies cutanées diminuent la qualité de vie quotidienne. Des problèmes psychologiques et cognitifs, tels la perte de mémoire, des difficultés de concentration et la souffrance émotionnelle, souvent associés à l'anxiété et la dépression, empêchent souvent les patients de vaincre les séquelles d'une maladie de Cushing pourtant guérie. Des études récentes rendent compte d'anomalies structurelles diffuses au niveau du système nerveux central en cas de d'hypercorticisme actif, qui seraient dues à la large répartition cérébrale des récepteurs glucocorticoïdes. Ces anomalies sont améliorées par la thérapie, mais le retour au normal est souvent incomplet. Il est donc fortement

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souhaitable que la durée d'exposition à la maladie de Cushing active soit réduite, en réduisant le délai diagnostique, qui est souvent long, et en initiant rapidement un traitement adapté, tout en préparant le patient à faire face aux périodes difficiles, notamment au décours de la chirurgie. Ainsi, le patient peut se préparer à une certaine baisse de la qualité de la vie de tous les jours, mais vivre dans l'espoir d'une amélioration ultérieure, espoir qui est souvent lui-même de valeur thérapeutique.

Mots clés : Maladie de Cushing ; Perte de qualité de vie ; Comorbidités résiduelles ; Anxiété ; Dépression ; Coping

1. Introduction

Hypercortisolism, characteristic of active Cushing's syndrome (CS) determines a host of invalidating signs and symptoms, which negatively impact on patients' health-related quality of life (QoL). These include physical problems like weight gain leading to central obesity, muscle weakness and fatigability, bone fractures, hypertension, skin abnormalities (thinning, easy bruising, red striae, ulcerations) as well as psychological impairment (bad memory, emotional distress, anxiety, depression, etc). Even though surgery with or without additional medical therapy can lead to control of hypercortisolism, often signs and symptoms typical of active hypercortisolism do not revert completely; this is so in Cushing's syndrome (CS) of any aetiology (adrenal, pituitary-dependent Cushing's diseases – CD−, or ectopic ACTH secretion), and determines persistent impairment of QoL, despite being considered endocrinologically "cured" [1].

This prior chronic exposure to endogenous glucocorticoid [GC) excess in CS is also associated with greater morbidity and mortality, related to complications such as components of the metabolic syndrome, cardiovascular events, muscle weakness, bone fractures, neurocognitive impairment and psychiatric disorders [2]. Thus, after resolution of hypercortisolism, patients still often complain of physical and psychological impairment [3], including cognitive changes, depression, less self-confidence and altered illness perception. All this determines a slow and incomplete recovery, severely affecting QoL even long-term after control of cortisol excess [1]. This is a matter of concern for many patients and their partners [4–6] and a challenge for clinicians. To further improve their outcome, patient-reported outcome measures are worth considering, as well as self-management programmes to enhance self-efficacy, as recently shown in a clinical trial [7].

Early detection of hypercortisolism to reduce the delay to diagnosis, and effective treatment aimed at achieving persistent remission is mandatory in CS patients to improve long-term prognosis and QoL [1]. Life-long evaluation with periodic laboratory and clinical assessment, is also highly recommendable even long-term after remission, to appropriately manage comorbidities (diabetes, hypertension, dyslipidemia) according to current guidelines.

2. The concept of health-related quality of life (QoL)

QoL is a patient-reported outcome measure, which can be evaluated with generic or disease-generated or specific questionnaires. It reflects the individual patient's definition of wellbeing, including perceptions of physical, psychological, emotional and social health issues. Disease–generated questionnaires tend to be more sensitive in identifying limitations specific of the disease, as well as changes after treatment, but cannot be used in normal subjects or in other diseases, while generic questionnaires are useful in any population, and allow comparing QoL in different diseases or with normal subjects. "Domain-specific" questionnaires are designed to evaluate a determined problem, for example, fatigability, pain, dyspnoea or sexual dysfunction, and are therefore useful to compare the degree of impairment of a specific domain [1].

Table 1
Psychological phases of adaptation.

1st phase: uncertainty and confusion
2nd phase: bewildered/Negation
3rd phase: opposition/Isolation
4th phase: rage
5th phase: sadness, which leads to either depression, or adaptation (the latter is easier if you are positive!)

Thus, after psychometric validation and translation into the languages of the patient populations to be investigated, QoL scores can be used to highlight the patient's impression on clinical aspects often not approached clinically, despite being important for everyday life [8], and complement the biochemical and radiological tests routinely used in patient's follow-up.

3. Effect o chronic hypercortisolism on health-related quality of life

With the availability of two different Cushing-specific QoL questionnaires (CushingQoL [9] and Tuebingen CD-25 [10,11]), new knowledge on impairment suffered by CS patients has emerged. CushingQoL consists of 12 questions with a five option Likert scale answer, which was described as unidimensional [12]. Recently, however, two subscales (psychosocial issues and physical problems) were identified and showed adequate model fit. Data were obtained from patients in remission from CS ($n = 341$) recruited from the Cushing's Syndrome Research Foundation's email lists; they completed the CushingQoL questionnaire and a short demographics survey [13]. Regardless of the scoring solution used, it was concluded that CushingQoL had proven to be a valuable resource for assessing health-related QoL in patients with CS (Table 1).

The Tuebingen CD quality of life inventory (Tuebingen CD-25) [10,11] is a 25-item questionnaire covering six essential

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