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Psychiatric and neurocognitive consequences of endogenous hypercortisolism

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Abstract. Piasecka M, Papakokkinou E, Valassi E, Santos A, Webb SM, de Vries F, Pereira AM, Ragnarsson O (University of Gothenburg; Sahlgrenska University Hospital, Gothenburg, Sweden; Hospital Sant Pau, Univ Autonoma de Barcelona; Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBER-ER, Unidad 747), ISCIII; Barcelona, Spain; Leiden University Medical Center, Leiden, The Netherlands). Psychiatric and neurocognitive consequences of endogenous hypercortisolism (Review). *J Intern Med.* 2020; **288**: 168–182.

Psychiatric and neurocognitive symptoms due to hypercortisolism were already described by Harvey Cushing in his original paper on patients with Cushing's syndrome (CS). Nowadays, it is well known that psychiatric and cognitive complaints are two of the most common, and most distressing, symptoms in patients with CS. Psychiatric symptoms are indeed a major clinical manifestation of CS. The most commonly observed psychiatric conditions are depression and anxiety, whilst mania and psychosis are less common. Several domains of cognitive function are impaired at diagnosis, including episodic and working memory, executive function and attention. Following treatment, one-fourth of the patients still experience depressed mood, and the cognitive impairments are only partially restored. Consequently, quality of life in patients with CS is severely and persistently affected. Neuroimaging studies have also illustrated the deleterious effects of hypercortisolism on the brain by demonstrating reduced grey matter volumes and cortical thickness, altered resting-state functional responses and during cognitive tasks, as well as widespread reduced white matter integrity, especially in structures important for cognitive function and emotional processing, both before and after successful abrogation of hypercortisolism. In this paper, we summarize the current knowledge on the psychiatric and neurocognitive consequences of hypercortisolism in patients with CS, both before, and after successful treatment. In addition, we review the structural and functional brain abnormalities associated with hypercortisolism and discuss the influence of these factors on quality of life.

Keywords: Cushing's syndrome, depression, cognitive dysfunction, neuroimaging, quality of life.

Introduction

Already in his original article on pituitary basophilism, Harvey Cushing described the psychiatric and neurocognitive consequences of hypercortisolism [1]. One of the patients, a 30-year-old man with typical cushingoid features, found himself without energy, was easily fatigued, was unable to concentrate his mind on his work, complained about forgetfulness and had fits of unnatural irritability that alternated with periods of depression [1].

Nowadays, it is well known that psychiatric and cognitive complaints are two of the most common and the most distressing symptoms in patients with Cushing's syndrome (CS). In a recent survey, including 164 patients with CS, fatigue, sleep disturbances, anxiety and depression, together with weight gain and muscle weakness, were the most common and most bothersome signs and symptoms related to CS [2]. Moreover, following treatment for CS, 90% of the patients still experienced symptoms, with fatigue being the single most common complaint [2].

The purpose of this paper is to summarize the current knowledge on the psychiatric and neurocognitive consequences of hypercortisolism in

patients with CS, both before, and after successful treatment. In addition, we review the structural and functional brain abnormalities associated with hypercortisolism and discuss the influence of these factors on quality of life (QoL).

Psychiatric symptoms

Affective disorders have been identified as a major clinical manifestation of CS [3,4]. The most commonly observed psychiatric disorders in patients with CS are depression and anxiety, whilst mania and psychosis are less common. In a study by Kelly et al., including 209 patients with active CS of all ages, depression, evaluated by clinical interviews and standardized questionnaires, was present in 57% of the patients [5]. Pathological anxiety was diagnosed in 12% of the patients, mania or hypomania in 3% and psychotic illness in 8%. Interestingly, symptoms due to psychiatric illness, mainly depression, were the first sign of CS in 12% of the patients. In another study by Sonino et al., 88 out of 162 (54%) patients with active Cushing's disease (CD) had major depression according to the DSM-IV criteria. Furthermore, depression was associated with high urinary cortisol concentrations and the severity of the syndrome [6]. In one further study, general anxiety was the most common affective disorder, present in 79% of the patients, followed by depression in 68% and panic disorder in 53% [7].

Four longitudinal studies have been conducted in patients with CS, showing that psychopathological problems improve, but do not resolve, after successful treatment. In the first prospective study, 72% of patients with CS reported an improvement of depressed mood following treatment [4]. Similarly, Sonino et al. reported that 70% of patients with CS fully recovered from depression after treatment, but 30% did not [8]. In another study, using a semi-structured interview and questionnaires, psychiatric disorders were present in 35 of 45 (81%) patients with active CS, with depression being the most common disorder [9]. Of 25 patients investigated following treatment, 8 (32%) still fulfilled the criteria for a psychiatric disorder [9]. In the fourth study, with the most rigorous protocol, Dorn et al. evaluated 33 patients with CS by using interviews and questionnaires before treatment, as well as 3, 6, and 12 months after remission [10]. Significant psychopathology, mainly atypical depressive disorder, was observed in 67% of patients before treatment, 54% at 3 months, 36% at 6 months and 24% at 12 months after remission. In other words, one-fourth of patients with CS still suffered from psychiatric illness one year after remission had been achieved.

Recent cross-sectional studies have also shown that patients with CS in long-term remission have an increased prevalence of psychopathology, evaluated with validated questionnaires, compared with controls [11-13]. In a study from the Netherlands, patients with CD in remission for a median of 11 years scored worse concerning apathy, irritability and anxiety and had more often maladaptive personality traits than matched healthy controls and patients treated for non-functioning pituitary macroadenoma [11]. Similarly, in a study from Spain, after a mean time of 6 years in remission, patients treated for CS frequently had problems with depression, anxiety and stress perception compared with controls [12]. Interestingly, the scores for the affective alterations were associated with serum concentrations of brain-derived neurotrophic factor, an important regulator of mood and stress [14]. Finally, Swedish patients, in remission for a median time of 13 years, were found to have higher scores for depression, anxiety and fatigue, compared with controls [13]. In the same cohort, problems due to mental fatigue, stress intolerability, irritability and emotional lability were much more common in patients in remission than in controls [15].

Affective symptoms seem to be less common in children with CS, as compared to adults. In 59 children and adolescents with active CS, mental and behavioural problems, including emotional lability, irritability or depression, were present in 19% [16]. In another study, one-fourth of 21 children with CD in remission had long-term psychiatric comorbidities [17].

Thus, mental illness is a common and serious comorbidity in patients with CS, both during the active stage of the disease as well as during long-term remission. In fact, in a recent large epidemiological study, 6 of 133 (5%) observed deaths amongst patients with CD were due to suicides [18]. Evaluation of mental status is therefore of fundamental importance, both at diagnosis and during long-term follow-up after treatment, especially since patients with CS may be prone to conceal serious psychiatric symptoms, including suicide attempts [19].

Cognitive function

The first studies on cognitive function in patients with CS were published in the early 1980s when Monica Starkman and colleagues described memory impairments in 83%, and concentration difficulties in 66% of patients with active hypercortisolism [4,20]. Later, the same authors demonstrated an association between reduced hippocampal volume and memory impairment [21], and that functional improvement in memory encoding occurred one year following treatment [22]. Numerous cognitive functions other than memory are also affected in patients with active CS, including visuospatial processing, reasoning and concept formation, executive functioning and attention [23,24].

Mauri et al. showed that memory functions were impaired in 25 patients with active CD compared with matched controls, and that improvement occurred in the 8 patients studied prospectively 6 months after correction of the hypercortisolism [25]. Similarly, Starkman and colleagues observed that verbal fluency and verbal recall improved 18 months following successful surgery in a cohort of 27 patients with CD [26]. On the contrary, two additional prospective studies, including 13 and 33 patients with CS, respectively, did not observe improved cognitive function one year postoperatively [27,28]. Furthermore, in the most recent prospective study on 18 patients, only limited improvements in executive function and attention were seen 3 years after treatment [24].

Cross-sectional studies on patients with CS in remission have also demonstrated residual cognitive impairments at long-term follow-up as compared to controls. In a group of 74 patients with CD in remission for a mean time of 13 years, memory and executive functions were impaired, both compared with healthy controls, matched for age, gender and education, as well as patients with nonfunctioning pituitary macroadenoma [29]. Similarly, in another cohort deficits in attention, spatial orientation, alertness, working memory, verbal fluency and reading speed were observed in 55 patients with CS in remission for a median time of 13 years [13]. Furthermore, worse verbal and visual memory [30], as well as impaired decision-making [31], at long-term follow-up have been reported.

Neuroimaging

Cortical brain atrophy and ventricular enlargement in patients with active CS were first described in autopsy studies [32], and later by using pneumoencephalography [33]. Since then, several studies, using modern methodology on larger cohorts, have confirmed these adverse structural effects of hypercortisolism on the brain [34-36]. In the first studies using magnetic resonance imaging (MRI), patients with active CS were found to have decreased hippocampus volume in comparison to healthy individuals [21], and that the volume increases, but does not normalize, following remission [22,37]. The same findings were reported in a recent meta-analysis [38]. Cerebral atrophy has also been observed in patients with active CS, both in adults [39,40] and in children [41], which was only partially reversible following treatment. Other findings in active CS patients involve smaller volumes in comparison to healthy controls of several brain structures, including grey matter volumes of the medial frontal gyrus [42], cerebellar cortex and grey matter volumes [43], right amygdala volumes [36] and total amygdala volumes in children [41]. Furthermore, cross-sectional studies including patients with CS in remission have demonstrated reduced cortical thickness in several regions in the prefrontal cortex [31], smaller grey matter volumes in the anterior cingulate cortex [31,44] and greater volume of the bilateral caudate nucleus [42].

During the last decade, several studies have used functional MRI (fMRI) to investigate brain activity in patients with CS (Table 1). By using fMRI, haemodynamic changes during task performance, or at rest, are used to visualize brain activity [45]. In a study on adolescents (10–18 years ole) with active hypercortisolism, increased amygdala and hippocampus activation during memory encoding were observed [46]. Also, adults with active CS, who make more errors during discrimination of facial expressions as compared to controls, have lower activation in the left anterior superior temporal gyrus, a region important for emotional processing [47].

Equally interesting are recent fMRI studies performed on patients in remission showing lower activation of the medial prefrontal cortex in patients compared with controls during processing of emotional faces [48], as well as reduced functional responses in the prefrontal cortices during episodic and working memory tasks (Fig. 1) [49]. Furthermore, two studies have investigated brain activity in patients in remission during rest, (resting-state fMRI), that is, when the participants are

Table 1. *Summary of studies in patients with Cushing's syndrome (CS) using functional magnetic resonance imaging (MRI)*

Author Year (Ref)	Origin	Design/Methods	No. of subjects	Duration of remission (years)[a]	Main findings	Comments
Maheu 2008	USA	Cross-sectional. Amygdala and anterior hippocampus activation measured during emotional faces encoding task.	12 adolescents with active CS 22 healthy controls	-	Greater left amygdala and right anterior hippocampus activation during face encoding in patients.	
Langenecker 2012	USA	Cross-sectional. Facial Emotion Perception Test.	18 active CS 21 healthy controls	-	Patients had more errors in categorizing facial expressions, and lower activation in left anterior superior temporal gyrus, a region important in emotional processing.	
van der Werff 2014	The Netherlands	Cross-sectional. FA of white matter examined by using diffusion tensor imaging.	22 CD in remission 22 healthy controls	12±8	FA reductions in cingulate cingulum, uncinate fasciculus and corpus callosum, in patients. Severity of depression symptoms negatively associated with FA in the left uncinate fasciculus.	Same cohort as in van der Warff 2015 and Bas-Hoogendam 2015
van der Werff 2015	The Netherlands	Cross-sectional. Brain activation during rest.	24 CD in remission 24 healthy controls	11±9	Patients with CD: increased RSFC between the limbic network and the anterior cingulate cortex as well as increased RSFC of the default network in the left lateral occipital cortex.	Same cohort as in van der Warff 2014 and Bas-Hoogendam 2015
Bas-Hoogendam 2015	The Netherlands	Cross-sectional. Brain activation during emotion processing using pictures of emotional faces.	21 CD in remission 21 healthy controls	11±8	Lower activation of the medial PFC during processing of emotional faces and decreased functional coupling between the ventromedial PFC and posterior cingulate cortex in patients.	Same cohort as in van der Warff 2014 and 2015

Table 1 (*Continued*)

Author Year (Ref)	Origin	Design/Methods	No. of subjects	Duration of remission (years)[a]	Main findings	Comments
Pires 2015	Spain	Cohort and cross-sectional. White matter changes examined by diffusion tensor imaging.	8 active CS 7 controlled CS on medical treatment 20 CS in remission 35 controls.	6±7	Widespread white matter alterations indicating loss of integrity and demyelination in patients with CS, both active, cured and medically remitted. No correlations with urinary free cortisol or disease duration.	
Ragnarsson 2017	Sweden	Cross-sectional. Brain activation during episodic and working memory tasks.	19 CS in remission 19 healthy controls	7 (6–10)	Lower functional brain responses in the left and right PFC bilaterally in patients during episodic memory encoding and retrieval, as well as during a working memory task.	
Jiang 2017	China	Cross-sectional. Brain activation during rest.	18 active CS 14 CS in remission 22 controls	5±3	Widespread altered spontaneous brain in patients with active CS, including the posterior cingulate cortex and the left PFC. Trends for partial restoration after treatment in several brain regions.	
Stomby 2019	Sweden	Cross-sectional. Brain activation during rest.	19 CS in remission 19 healthy controls.	7 (6–10)	Elevated RSFC in the MTL and PFC networks amongst patients with CS. The degree of connectivity in the MTL negatively associated with time in remission.	Same cohort as in Ragnarsson 2017

CD, Cushing's disease; CS, Cushing's syndrome; FA, fractional anisotropy; MTL, medial temporal lobe; PFC, prefrontal cortex; RSFC, resting-state functional connectivity.
[a]Presented as mean ± standard deviation or median (interquartile range).

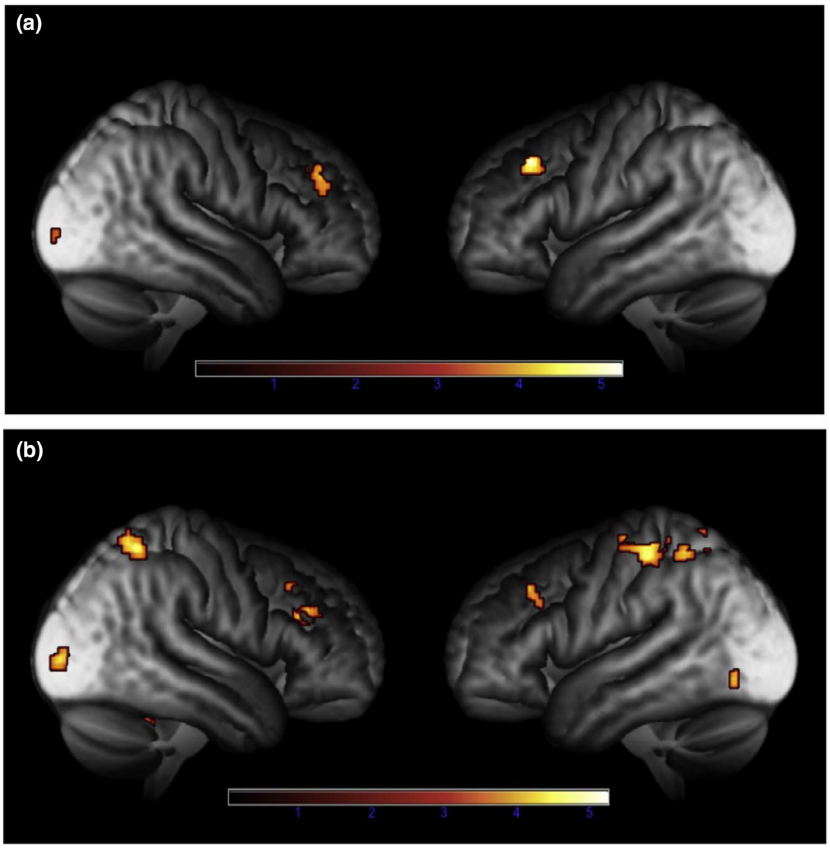

Fig. 1 *Brain areas with reduced functional brain responses during episodic memory (a) encoding and (b) retrieval in patients with Cushing's syndrome in remission as compared to healthy controls (Adapted from Ragnarsson O et al. Psychoneuroendocrinology. 2017; 82:117–25).*

instructed to lay still and stay awake without being presented to a stimulating task. In the first study, patients with CD had increased resting-state functional connectivity between the limbic network and the anterior cingulate cortex, as well as of the default mode network in the left lateral occipital cortex [50]. In the second study, elevated resting-state connectivity was found in the medial temporal lobe (including the hippocampus) and the prefrontal cortex networks [51]. In one further resting-state fMRI study, widespread alterations in spontaneous activation were seen at diagnosis, including in the posterior cingulate cortex and the left prefrontal cortex, that were only partially restored after treatment [52].

Another MRI technique, diffusion tensor imaging (DTI), has recently been used to study white matter integrity, architecture and microstructural abnormalities in patients with CS (Table 1). In a study by van der Werff et al., widespread decreased white matter integrity was observed in patients in remission compared with healthy controls [53]. Similarly, Pires et al. found diffuse white matter changes in both patients with active CS and patients in remission, suggesting an underlying loss of white matter integrity and demyelination [54]. Interestingly, van der Werff et al. observed that the degree of reduced integrity in the uncinate fasciculus, that is a white matter connection between the limbic system and the frontal lobes, was related to depressive symptoms [53]. Similarly, Pires et al. found that the DTI alterations in patients with CS were related to both depressive symptoms and cognitive function (information processing speed) [55]. Furthermore, high degree of white matter lesions, similar to those

associated with cognitive decline in the elderly, has been demonstrated in patients in remission [56].

Finally, concentrations of neurotransmitters in the brain can be measured with an additional MRI technique called proton magnetic resonance spectroscopy. By using this technique, patients with CS in remission were shown to have lower N-acetyl-aspartate and higher glutamate/glutamine concentrations in the hippocampus as compared to controls, indicating neuronal loss and glial proliferation, respectively [57]. With the same method, lower concentrations of glutamate (an important excitatory neurotransmitter) and N-acetyl-aspartate (a marker of neuronal integrity) were observed in the ventromedial prefrontal cortex of patients with CS (active and patients in remission analysed as one group), and that the concentration of both neurotransmitters was associated with anxiety and duration of hypercortisolism [58].

Sleep

Although insomnia and other sleep disturbances were already described in the original paper on patients with CS [1], sleep quality in these patients has not yet been satisfactorily explored. Accordingly, the influence of sleep disturbances on psychological and cognitive dysfunction, as well as QoL, remains to be clarified (Table 2).

In early studies, 50% of patients with CS were found to have sleeping difficulties, for example middle night insomnia and early morning awakenings [4]. Also, studies using electroencephalography on small groups of patients with active CS showed impaired sleep continuity, increased awake time, lighter and more fragmented sleep, decreased slow delta wave sleep and shortened rapid eye movement (REM) latency [59-62]. Furthermore, higher cortisol concentrations in plasma and urine were associated with lower REM activity, longer awake time and lower sleep maintenance [62]. More recently, D'Angelo et al. demonstrated a more fragmented sleep and an increased nocturnal motor activity in patients with CS as compared to healthy controls using wrist actigraphy [63].

In the first study on obstructive sleep apnoea in patients with active CS, Shipley et al. found a prevalence of 32% (seven of 22 subjects), of whom four had clinically significant disorder [61]. More recently, by using overnight polysomnography, Gokosmanoglu et al. found the prevalence of obstructive sleep apnoea in a small group of young female patients with newly diagnosed CS to be 50%, compared with 23% in matched controls [64]. In that study, serum cortisol concentrations were independently associated with Apnoea–Hypopnoea Index, after controlling for BMI [64]. Finally, a threefold increased risk for obstructive sleep apnoea was noted in a large cohort of patients with CS [65]. However, in that study, neither the diagnosis nor the aetiology of the syndrome was validated, and information on remission status was missing.

Taken together, patients with active CS seem to have poor sleep quality and a high prevalence of obstructive sleep apnoea. Nevertheless, the studies presented above are limited by small sample size, and studies on sleep disturbances in patients with CS in long-term remission are currently lacking.

Quality of life

Patients with CS have consistently been found to have impaired QoL, both before and after treatment, and both when evaluated with generic as well as with disease-specific questionnaires [38,66]. Many of the adverse effects of hypercortisolism on the brain, such as depression [12,67,68], anxiety [68,69], negative illness perception [70] and poor coping strategies [71,72], have indeed been identified as major determinants of the poor QoL [73].

QoL in patients with active CS is strikingly poor [67,74,75]. QoL improves following treatment, where remission is the strongest factor associated with the improvement [75-77]. This was clearly illustrated in a recently published large longitudinal study from the ERCUSYN, where QoL was evaluated at diagnosis, 1 year after surgery and at long-term follow-up (median 3 years), in 595 patients with CS [76]. At long-term follow-up, the disease-specific Cushing QoL score in patients with CD was low (indicating worse QoL) compared with scores in patients with CS of adrenal origin. However, after adjustment for remission status, no difference was seen between the groups.

Nevertheless, QoL after treatment is still impaired, both when compared to healthy subjects, as well as to patients with other types of pituitary adenomas [78]. In a cross-sectional study by van Aken et al., both physical and psychosocial impairments were observed in 58 patients with CD in remission for a

Table 2. *Summary of studies investigating sleep quality in patients with Cushing's syndrome (CS).*

Author Year	Origin	Study period	Design/Methods	No. of patients	Active disease/ remission	Main findings	Comments
Krieger 1974	USA	Not specified	Cohort study. Sleep quality evaluated by using overnight PSG and EEG.	26	Active disease and remission	Reductions of sleep stages III-IV in 4 patients in remission and 6 patients with active CS. Normalization after adrenalectomy in 16 patients with adrenal adenoma.	Heterogonous group: active CS, patients in remission, patients on high dose glucocorticoid therapy.
Shipley 1992	USA	Not specified	Cohort study. OSA and sleep quality evaluated by using overnight PSG.	22	Active	32% of CS patients had OSA. 18 % had clinically significant OSA. Even nonapnoeic patients had lighter, and more fragmented sleep, compared with controls. Shorter REM latency and increased REM density in patients.	17 patients with ACTH-dependent CS and 5 with adrenal tumour.
Friedman 1999	USA	Not specified	Cohort study. Sleep quality examined by using PSG.	12	Not specified	Less delta sleep in patients with CS compared to healthy controls.	9 patients with CD and 3 with ectopic ACTH syndrome.
D'Angelo 2015	Italy	Not specified	Cohort study. Wrist actigraphy on 3 consecutive days used to evaluate sleep quality and sleep duration.	12	Active	Fragmented sleep and increased nocturnal motor activity more frequently seen in patients with CS compared with 12 healthy controls.	
Wang 2017	Taiwan	1998–2009	Register study based on ICD codes from a National Health Insurance Research Database.	1612	Not specified	Threefold increased risk of OSA in patients with CS compared with controls.	No information on aetiology of CS, treatment or remission status. Diagnosis of CS not validated.

Table 2 (*Continued*)

Author Year	Origin	Study period	Design/Methods	No. of patients	Active disease/ remission	Main findings	Comments
Gokosmanoglu 2017	Turkey	2014–2015	Cohort study. Apnoea–Hypopnoea Index score measured by using overnight PSG.	30 women	Active	Prevalence of OSA higher in patients (50%) with CS compared with 30 female controls (23%) matched for age and BMI.	

ACTH, adrenocorticotropic hormone; BMI, body mass index; CD, Cushing's disease; CS, Cushing's syndrome; EEG, electroencephalography; ICD, International Statistical Classification of Diseases and Related Health; OSA, obstructive sleep apnoea; PSG, polysomnography; REM, rapid eye movements.

mean time of 13 years, compared with healthy controls [69]. Similarly, Lindsey et al. showed a reduced mental and physical QoL in 343 patients with CS in remission for a median of 3 years [74]. Furthermore, in a recent systematic review, patients with CD indeed had the worst QoL at diagnosis, and the smallest improvement after treatment, compared to patients with nonfunctioning pituitary adenoma, acromegaly and prolactinoma (Fig. 2) [78]. Finally, a recent meta-analysis including data from 37 studies on QoL, of whom 15 contained data before treatment and 34 after treatment, confirmed that QoL improves, but does not normalize after treatment [79].

Some of the factors that are associated with poor QoL in patients with CS, such as depression and anxiety, are modifiable [73]. Also, influencing the illness perceptions and coping strategies of patients with CD may be beneficial [70-72]. Interestingly, a specific educational programme for patients with CS resulted in improved physical activity, healthier lifestyle, better sleep patterns and reduced pain, that subsequently contributed to an improved QoL [80]. In another interesting study, promising results were observed when a self-management intervention, with a focus on the social and psychological issues, was applied in patients with pituitary diseases, including CD, and their partners [81].

Potential reasons for incomplete recovery after successful treatment

Considering the above, a substantial body of evidence indicates that the negative effects on the brain in patients with CS are not completely reversible following successful treatment and restoration of normal cortisol exposure. The underlying mechanisms are not completely understood, although an irreversible neurotoxic effect of the hypercortisolism itself seems to be likely. This is, in fact, supported by animal models demonstrating a deleterious effects of chronic glucocorticoid excess on the hippocampus and the prefrontal cortex [82,83]. This hypothesis is also supported by studies showing that longer duration of hypercortisolism, that is diagnostic delay, is associated with structural brain abnormalities [34], worse QoL [12,74,84,85], depression [12] and adverse brain metabolite profile [58]. Further support comes from studies showing that aetiology of the hypercortisolism, that is whether it is caused by CD or cortisol-producing adrenal adenoma, does not seem to be of importance [5,8,13]. However,

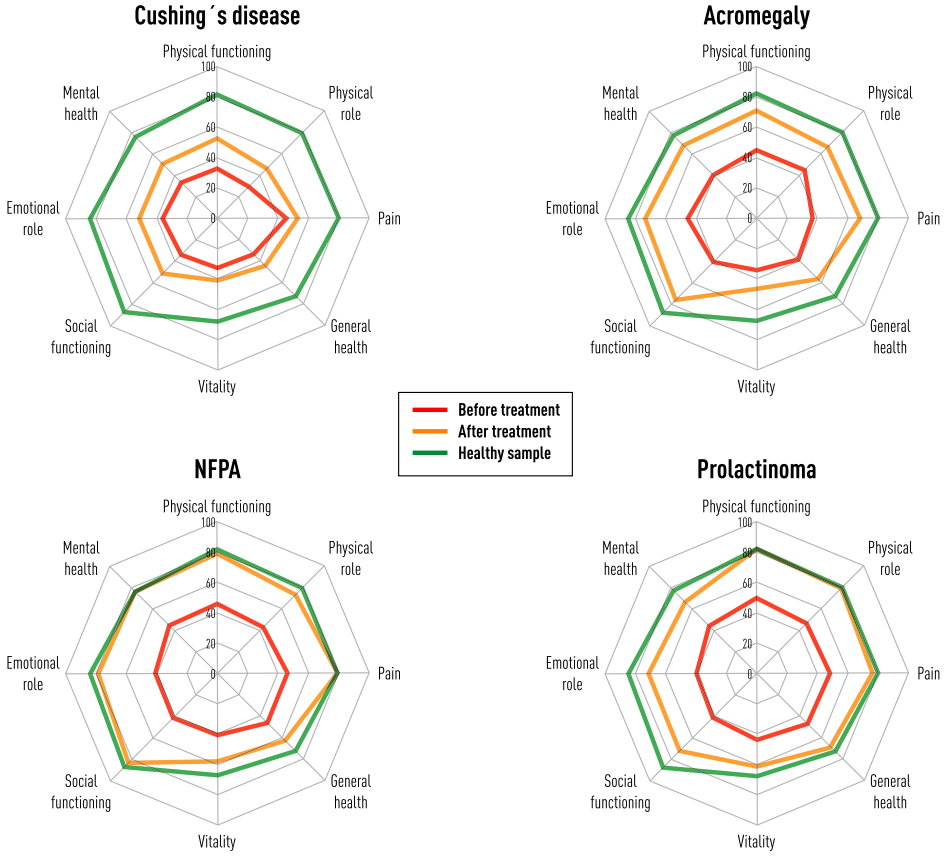

Fig. 2 *Quality of life in patients with (a) Cushing's disease, (b) acromegaly, (c) nonfunctioning pituitary adenoma and (d) prolactinoma, before (red line) and after treatment (blue line), in comparison to healthy controls (green line) (Adapted from Andela CD et al. Pituitary. 2015; 18:752–76).*

other possible explanations may exist and are discussed below.

Influence of treatment

Hypopituitarism, including adrenal insufficiency, hypothyroidism, hypogonadism and growth hormone deficiency, may all affect cognitive function, mental health and QoL. In a recently published epidemiological study, more than half of all patients with CD in remission had at least one pituitary hormone deficiency at long-term follow-up [18]. Pituitary radiation, one of the second-line treatment alternatives for patients with CD, may also have adverse effects on neurocognitive function in patients with pituitary adenoma [86-88].

The currently available literature concerning the effects of hypopituitarism and radiotherapy on outcome in patients with CD is inconsistent. Hypopituitarism has been found to be associated with impaired QoL in some studies [69,85], but not in another [84]. Surprisingly, radiotherapy was found to be associated with better QoL in a large study [85], but other studies could not confirm this association [69,74]. However, most studies published to date are underpowered, and further studies are needed to explore the influence of treatment and hormone deficiencies on psychiatric and neurocognitive status in patients with CS.

Genetics and epigenetics

The effects of cortisol in the human body are mediated via two receptors, the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR). The MR is either aldosterone-selective (in the kidney), or cortisol preferring, depending on

the tissue-specific expression of intracellular enzymes that convert cortisol into inert cortisone (and vice versa): the 11-beta-hydroxysteroid dehydrogenases (11-beta HSD) type 2 and -1, respectively. MRs are prominent in the brain whereas 11-beta HSD2 is virtually not expressed, consequently, the effects of cortisol in the brain depend on the balance between MR and GR activation [89].

Cortisol exposure is further regulated by various other pre- and postreceptor enzymes, transmembrane transport systems and intracellular proteins, such as the FK506 binding protein 5 (FKBP5), that regulate sensitivity of the glucocorticoid receptor. Several polymorphisms in both the MR and the GR gene affect its sensitivity [90]. In patients with CS, common polymorphism in the glucocorticoid receptor gene (Bcl1), as well as in the gene coding for 11-beta-hydroxysteroid dehydrogenase type 1, has been found to be associated with cognitive dysfunction (Fig. 3) [91]. Bcl1 has also been found to be associated with adverse cardiometabolic risk factor profile [92] and reduced bone mineral density [93,94] in patients with CS in remission, and higher BMI in patients with active disease [95].

Reduced global DNA methylation was recently demonstrated in patients with CS in remission [96]. Numerous genes that were differently methylated in patients as compared to controls were associated with scores for depression, anxiety and/or fatigue. Of special interest was that the gene coding for FKBP5, an important regulator of the glucocorticoid receptor function, was specifically hypomethylated. Similar hypomethylation of the FKBP5 gene was found in another cohort of patients with CS, and that the hypomethylation was associated with hippocampal volume [97].

Conclusions

Hypercortisolism, as it presents in patients with CS, has deleterious effects on the central nervous

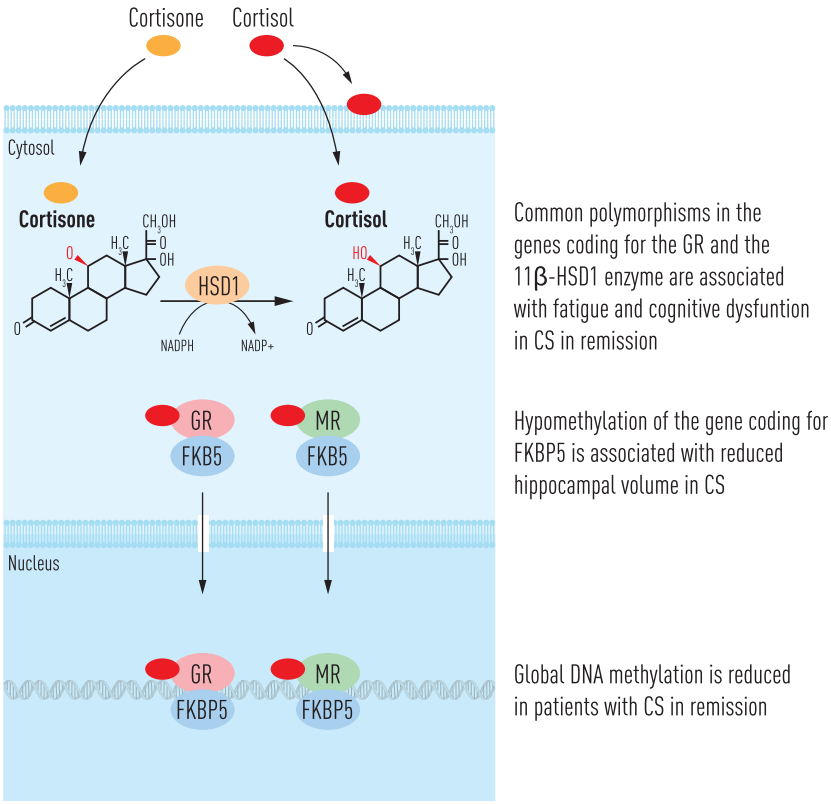

Fig. 3 *Summary of the influence of genetic and epigenetic alterations on the brain in patients with Cushing's syndrome.*

system, causing irreversible structural and functional brain alterations, psychiatric complications, cognitive impairments and subsequently impaired QoL. Although the chronic effects of hypercortisolism on the brain are apparently widespread and diffuse, the effects on the hippocampus and the prefrontal cortex, brain regions that are especially rich in glucocorticoid receptors, and important for cognitive function, seem to be most prominent [98]. The major limitations of the current literature on the effects of hypercortisolism on the brain are the small cohorts and the lack of longitudinal follow-up data, that is studies where brain function, in its widest meaning, is studied before, as well as during long-term follow-up after treatment in patients with endogenous CS.

Disclosure summary

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