The Relationship of Endogenous Cortisol to Psychiatric Disorder: A Review

Stephen J Kiraly, MD, FRCPC, Raymond J Ancill, MB, MRCPsych, FRCPC, Gergana Dimitrova, MD

Objectives: To focus on hypothalamic-pituitary-adrenal (HPA) axis activity, especially endogenous hypercortisolemia, to study its role in the maintenance of psychiatric illness, and to entertain the probability that the elderly are vulnerable.

Method: Case presentation, clinical and research literature review, and theoretical discussion.

Results: Clinical and research evidence overwhelmingly suggest that hypercortisolemia is toxic to the hippocampus. Some research supports the position that it can be a treatable perpetuating factor in a subset of affective disorders and psychoses. Pharmacological treatments to correct hypercortisolemia have been used by endocrinologists. Hypercortisolemic treatment-resistant and nontreatment-resistant psychoses and affective disorders have been successfully treated by a small number of researchers who remain interested in this subject. Data pertaining to geriatric psychoses may be germane but are sparse.

Conclusions: It behooves us to research diagnostic methods pertaining to psychoses and affective disorders associated with hypercortisolemic states. Very little research is available, but we must be alert to the possibility that the elderly are more susceptible to cortisol endotoxicosis than the younger adult population. Without accurate diagnosis, we cannot take advantage of existing antiglucocorticoid strategies.

(Can J Psychiatry 1997;42:415–420)

Key Words: depression, geriatric psychiatry, glucocorticoids, hypercortisolemia, psychosis, stress, treatment resistance

The effects of steroid hormones, testicular hormones in particular, were studied as early as 1849 by Berthold, who, by performing the first formal experiment relating behaviour to endocrine function, opened the doors to the science of neuroendocrinology (1). Asher’s famous paper entitled “Myxoedematous Madness,” published in 1949, alerted a generation of physicians to the interaction between the brain and the thyroid gland (2). As a result, we now screen both young and elderly psychiatric patients for thyroid malfunction. Cushing, in 1913, jumped to the erroneous conclusion that each endocrine disorder had “its peculiar symptom-complex and its more or less characteristic mental deviations,” but he correctly maintained that “psychic conditions profoundly influence the discharges from the glands of internal secretion” (3). He discovered hyperadrenalism and described the syndrome, now named after him, characterized by the presence of “sleeplessness, inability to concentrate, visual disturbances” and “fits of unnatural irritability alternated with periods of depression” (4). Later, the introduction of tritiated steroid hormones produced knowledge about brain steroid receptors, their pathways, and other neurotransmitter substances. The brain was understood to be both a source and a target of adrenal and other steroid hormone activity (5). Despite these milestones, the adrenals and their glucocorticoid effects on brain structures have not had the same respect as the gonads and the thyroid.

The aged brain has diminished homeostatic reserve and is vulnerable to disturbances in internal milieu (6). Clinicians have observed cases of primary affective disorder, with or without delusions and agitation, which have occurred for the first time in old age (7–9). We have also observed many such cases on our psychogeriatric unit. The following case study exemplifies diagnostic and treatment issues.
Case Study

EC, an 87-year-old woman, suffered a number of serious life events, became overwhelmed and depressed, and moved to a retirement home. She became increasingly paranoid and agitated. She developed hypomanic behaviour and grandiose delusions, without delirium. History revealed no previous psychiatric disorder. Over the year prior to her decompensation, she had no difficulties with activities of daily living (ADL), coped as a caregiver to a dying husband, and was medically stable. At time of first admission, laboratory investigations revealed only hyponatremia, hypomagnesemia, and elevated serum cortisol, which was not suppressed with dexamethasone (DEX) treatment. There was some discussion among clinicians as to whether she appeared cushingoid, but consultation with endocrinologists did not yield the diagnosis of Cushing’s syndrome. She failed to respond to a number of antidepressant and neuroleptic medications and seized on lithium. Upon hospitalization, electrolyte imbalance was corrected and anticonvulsant medication was instituted. Brief, transient improvement was followed by relapse and a second hospitalization for electroconvulsive therapy (ECT). Improvement followed, with the return of a normal sleep pattern and euthymia. The patient’s cortisol levels and dexamethasone suppression test (DST) returned to normal. Computerized tomography (CT) scan results revealed a small, inoperable adrenal adenoma, but her serum cortisol level was now normal and she was asymptomatic. She was discharged to her nursing home, in a much improved condition, without further need for psychotropic medications.

Was this a case of subclinical Cushing’s syndrome? Was hypercortisolemia a causative or major perpetuating factor in the treatment-resistant psychosis?

Cushing’s Syndrome and Psychiatric Illness

The overlap between Cushing’s syndrome and affective disorder has been well documented in adults (10,11). Elevated cortisol levels, without the physical stigmata of Cushing’s syndrome, have been studied in a number of psychiatric disorders, for example, depression (12–16), mania (17), anxiety (18), dyssomnia (19), memory and cognitive impairments (20,21), and delusional depressive psychoses (22,23). Early researchers noted that the predisposing factors and vulnerability to depressive illness were correlated with those for Cushing’s disease and that mania and depression often preceded the physical signs of Cushing’s syndrome (24).

Neurotoxic Effects of Corticosteroids

Research data on elderly subjects are lacking, but general research suggests that wide fluctuations or prolonged elevation in glucocorticoid levels have neurotoxic effects. Sudden reductions may play a role in inflammatory brain disease, and normal levels may prevent stress-activated or toxin-mediated defence mechanisms from overshooting, causing inflammations such as encephalomyelitis (25). By contrast, an excess of circulating glucocorticoids has been noted to be associated with loss of receptors in the hippocampus, which is crucial in learning, memory, and emotion (26,27). The removal of the adrenal glands in the treatment of Cushing’s disease has also improved psychiatric symptoms such as depression (28). Cortisone reverses the mental symptoms of adrenal insufficiency (Addison’s disease) even when physical signs are absent (29). Adrenal steroid excess promotes traits associated with affective disorders such as anxiety, dysphoria, agitation, dyssomnia, and psychotic episodes (11,30). Medical Letter consultants both admonish and cite studies that indicate that exogenous corticosteroids, especially in high doses, can cause mania, depression, paranoia, confusion, hallucinations, and catatonia (31). Healthy, nongeriatric volunteer subjects were not profoundly affected by small doses of exogenous corticosteroids, but 75% reported sadness, restlessness, and confusion (20). In laboratory studies, several days of steroid treatment noticeably impaired memory in humans (32).

Hippocampus is Target of Neurosteroidal Activity and Toxicity

There is a consistent finding across the mammalian species that the hippocampal formation is the principal target for neurosteroidal activity (33–35). The hippocampus is the main constituent of the limbic system, and lesions in this area produce severe memory and attention deficits with serious affective and behavioural disturbances (36–38). Experimental work on the effect of neurosteroids on long-term potentiation (LTP) and kindling in the hippocampus suggests that these phenomena may serve as a model for cognitive disturbances found with hypercortisolemia and in depression (11). Within hormone-sensitive brain regions, steroid hormones activate the synthesis of specific proteins by binding to intracellular receptors. This is the well-established or classical genomic model of steroid action and enzyme induction. In addition, there are more recently discovered rapid (seconds or minutes) membrane receptor effects in conjunction with the slower (hours or days), much better-understood, intracellular, genomic actions (39). In rats, steroid hormones are multifunctional messengers to the brain with trophic estrogen and destructive corticosteroid effects to the hippocampus (33). There is a fundamental bimodal modulation of γ-amino-nobutyric acid (GABAγ) receptors that modulates a myriad of psychophysiological phenomena such as stress, anxiety, depression, aggression, and seizures (40). Chronically elevated glucocorticoid levels are associated with cellular loss in the hippocampi of mammals such as rats and monkeys (34). The hippocampus has also been found to be reduced in Cushing’s syndrome (34,41).

A review of major research into hippocampal energetics suggested that a high level of endogenous cortisol did not cause neuronal death directly but acted as an enabler by impairing the capacity of neurons to survive coincidental neurological insults such as hypoxia–ischemia, seizure, hypoglycemia, antimitabolites, and oxygen radicals (34).
On a more macroanatomical scale, there are a number of studies that suggested that gross cerebral atrophy accompanies steroid use. Cerebral atrophy has been reported in Cushing’s syndrome (42,43). Other studies have pointed out that patients who had been treated with high doses of steroids for poliomyelitis and collagen-vascular diseases have similar changes (44). In some cases, the atrophy appeared to be radiographically reversible upon discontinuation of the cause (43,44).

Although definitive studies are lacking, there is preliminary evidence that long-term torture victims in prison have developed psychiatric disorders and cortical atrophy on CT scans (35,45). Concentration camp survivors have been reported to show accelerated decline of cognitive function in later years (45,46). People with nonspecific head injury in young adulthood have also been reported to show accelerated cognitive decline in later years (47). We need to be cautious, however, about extrapolating the implications of such results to the geriatric population. To our knowledge, there are no studies of geriatric concentration camp survivors that show accelerated decline in cognitive function.

**Depression and Hypercortisolemia**

The transduction of psychosocial stress into neurobiological phenomena and affective disorders is germane to this topic. Early clinical observations (48,49) and a comparative review of recent systematic studies document strong evidence for the importance of psychosocial stressors in ushering in a first-episode major affective disorder (50).

The dysregulation of the HPA axis in Cushing’s syndrome, depression, and psychosis is a well-documented phenomenon (11). Researchers have found that dysregulation in depression differs from dysregulation found in Cushing’s syndrome. Normally, cortisol and other steroid hormones are secreted in bursts in a circadian cycle, with highest levels in the morning hours. The normal rhythm architecture is obliterated in the majority of cases of Cushing’s syndrome but not in major depression. The hypercortisolism of depression is characterized by higher amplitudes of secretory pulses and higher total cortisol secretion but not an increase in the number of pulses. Sleep disturbance consists of abnormally short rapid eye movement (REM) sleep latencies. In time, antidepressant drugs or ECT treatments are known to normalize levels of cortisol secretion. In particular, treatment lengthens REM latency (15,51). The age range of the patients in the Linkowsky and others’ study (51) was from 31 to 62 years, leaving room for speculation about the results of a similar study in the geriatric population. The psychiatric presentation of endogenous hypercortisolemia and symptoms of exogenous glucocorticoid administration are dissimilar (15), but cognitive impairments are demonstrable in normal subjects on administration of exogenous corticosteroids (20,52). Cortisol hypersecretion has been associated with cognitive impairment when age and depression were studied as independent variables (53). Further insight into the effects of suppression of serum cortisol may be gained from the response of depressed nongeriatric patients to short-term administration of low-dose DEX. In preliminary reports and double-blind trials, administration of DEX rapidly improved depression without producing euphoria or other side effects (54–56). In another sample of 7 bipolar patients ranging in age from 18 to 75 years, an 85% response rate was found to oral or intravenous DEX administration (57). In the 4 latter studies, serum cortisol levels were not reported; therefore, it is not clear how cortisol levels correlated with improvement in mental status.

The DST has been proposed as a biological marker for depression, but despite its high specificity, it has not proved useful because of low sensitivity (58). Other researchers have found that the hypercortisolemic response to the stress of hypoglycemia was preserved in depression but not in Cushing’s syndrome and that this was a reliable discriminatory test between the 2 conditions (59). To demonstrate adrenal insufficiency by insulin tolerance test, symptomatic hypoglycemia is necessary to produce an adequate cortisol response (60). This response would be absent in Addison’s disease but not in primary affective disorder.

**Cortisol Levels and Aging**

Adrenalectomized rats do not show the “normal” hippocampal cell loss associated with aging (61). In rats and primates, the hippocampus loses neurons with age: there is a gradual, hippocampal corticosteroid receptor loss resulting in decreasing feedback inhibition and age-related increasing serum cortisol levels (34,62,63). For the human hippocampus, the situation is similar in that there is age-related neuronal loss, but basal serum cortisol levels do not rise proportionately with age, at least not until about age 75. The impression that the aged hippocampus does not suffer dysfunction may be reflecting the sampling bias that 60- to 70-year-olds are “old.” Gerontologists usually consider those over 75 as “old.” Overall, basal cortisol levels and the stress response appear to be adequate and within normal values in humans up to about age 75, whereas rats show a steady age-related decline. In humans, this normalcy is maintained by opposing changes. There is an age-related decline in glucocorticoid production, with a similar age-related decline in clearance and excretion. The result is a longer half-life in the blood stream and lower urinary corticosteroid concentrations (26). There are, however, some subtle defects that are similar to those found in aging rats and baboons. Extremely aged humans tend to be hypercortisolemic and DST-resistant (26,64,65). When challenged with a lower dose (0.5 mg DEX) instead of the standard dose (1.0 mg DEX), the healthy aged are DEX-resistant at a higher rate than their young counterparts. In other words, the aged tend to be borderline feedback-resistant, and this frailty may make them susceptible to hypersecretion of cortisol. In addition, some diseases common in old age, such as depression and senile dementia of the Alzheimer’s type (SDAT), are associated with HPA dysregulation and hypercortisolemia independently of basal age-related changes (26). Patients with SDAT (and those with
Given that older adults perform most poorly in tasks which require effort and deeper semantic processing, are susceptible to interference from retroactive and proactive inhibition, and are more sensitive to distracters (52,64), the signs and symptoms of hypercortisolemia are most unwelcome. Regardless of its mechanism of action, hypercortisolemia has been associated with complications with the following frequencies: fatigue 100%, irritability 86%, memory problems 83%, weight gain 80%, depressed mood 77%, sleep disorder 69%, difficulty concentrating 66%, sexual dysfunction 69%, anxiety 66%, and crying 63% (10). These signs and symptoms are also commonly found in depression, SDAT, and other geropsychiatric syndromes (26,66).

**Diagnostic and Treatment Implications**

True Cushing’s syndrome has been successfully treated by cortisol antagonists (67–70). The rationale for using specific antiglucocorticoids in the treatment of major depression was reviewed recently, and the preliminary results of a small study were reported. In an open series, 4 patients with chronic, severe, treatment-resistant depression were treated with a glucocorticoid antagonist for up to 8 weeks. The mean scores on the Hamilton Depression Rating Scale for 3 patients decreased (71). Furthermore, review of the literature on hypercortisolemia as a factor in maintaining affective psychosis revealed cases of treatment-resistant affective psychosis, with or without Cushing’s disease, that have responded to cortisol antagonist therapy (59,72,73). In what may be the first open clinical trial of major clinical depression in the absence of Cushing’s syndrome, a study of 10 patients, all under age 65, provided evidence that corticosteroids were involved in the maintenance of sick affect and cognitive impairment. Ten patients satisfying DSM-III criteria for major depression and classified as treatment-resistant were included. Eight completed the study, which consisted of the discontinuation of other psychotropic drugs and 2 months’ treatment with steroid-suppressant drugs. Six subjects graduated as responders and 2 as partial responders. In 6 patients, the improvement has been maintained for over 5 months after withdrawing the drugs. Side effects were mild to moderate. The authors concluded that “the results provide some evidence that steroids are involved in the maintenance of depression, and that their suppression may lead to a readjustment of the hypothalamic–pituitary–adrenal axis with remission of depression.” They also pointed out that treatment-resistant patients form an important proportion (up to 28%) of the depressed population; this rather dramatic response is especially noteworthy. In the same sample, after recovery, some patients reported “being able to think more clearly” (74). Recently, in a case report of a 4-week, double-blind trial followed by a 14-week period of open-label treatment of refractory depression with an antiglucocorticoid, the authors reported a considerable reduction of depressive symptoms (75). In an open series of 8 patients who met the DSM-III-R criteria for major depression, cortisol synthesis inhibition was noted to normalize serotonergic subsensitivity while reducing ambient cortisol levels. Five patients recovered from their depression and the rest improved. The authors concluded that lowering serum cortisol was a safe and effective method of treating a subset of depressions and urged double-blind studies (76). These findings are consistent with previous experimental observations that corticosteroid receptors are downregulated in the brain with chronic stress (77). Upregulation of brain cortisol receptors may be important as a possible treatment intervention.

Unfortunately, none of the studies mentioned has focused on the increasingly common and difficult-to-treat affective psychoses in the elderly (over age 65) patient population.

There is experimental and observational evidence that adaptive coping responses can modulate HPA axis response to stressors. The availability of behavioural outlets, that is, efforts at affective or behavioural coping or control over a stressful stimulus or environment, is known to reduce HPA axis responses in rodents, primates, and humans (77–82). This finding has implications for residents of long-term care facilities and their caregivers. As Sapolsky remarked, “I can imagine few settings that better reveal the nature of psychological stress than a nursing home” (83, p 268).

Recently, it has been reported that HPA axis overactivity in panic disorders in nongeriatric patients can serve as a long-term treatment outcome predictor (84). Would similar effects be useful in predicting treatment outcome in depressed or psychotic geriatric patients?

One difficulty of using serum cortisol levels in diagnosing and following hypercortisolemic states is the rapid secretion and short half-life of cortisol. The resultant wide fluctuations of this hormone in the blood make individual random measurements difficult to interpret. Though more onerous to collect, 24-hour urine levels are more accurate. We are currently evaluating the efficacy of using fasting morning serum cortisol levels to screen for hypercortisolemia in patients admitted to our geriatric psychiatry unit. Dehydroepiandrosterone sulphate (DHEAS) has a much slower turnover and a resultant half-life of nearly a full day; it maintains a plasma level almost a thousandfold higher than cortisol. Extremely high levels (greater than 700 or 800 µg/dL) are suggestive of a hormone-secreting adrenal tumour. Elevated levels that are DEX-suppressible may also result from adrenal hyperplasia (85). The measurement of DHEAS levels, which originate almost entirely from the adrenals, has been found to be clinically useful in reflecting hypercortisolemia and its suppression by glucocorticoid biosynthesis inhibitors (personal communication, Murphy B, March 8, 1966).

**Conclusions**

Hypercortisolemia disrupts sleep, energy level, mood, and cognition. It is probable that the vulnerable, aged brain is as susceptible to the dangers of elevated endogenous cortisol levels as it is to the better-known deleterious effects of
exogenous steroidal antinflammatory drugs. Theoretically, by blocking cortisol biosynthesis and, more specifically, by producing cortisol receptor blockade in the hippocampus, the psychotoxic enabling effects of hypercortisolemia may be mitigated or prevented. Although research data on hormonal actions on brain steroid receptors in the aging population are sparse, there is some experimental evidence and clinical opinion pertaining to the younger adult population that rapid response can be obtained in a subset of depressions, with or without psychosis, by correcting HPA axis overactivity. Given that a number of relatively safe glucocorticoid antagonists are available, well-controlled follow-up studies of glucocorticoid inhibition in the treatment of psychiatric syndromes accompanied by hypercortisolemia are indicated.

In geriatric psychiatry, where low tolerance of standard treatment methods, such as psychotropic drugs and ECT, are often problematic and where treatment resistance is not uncommon, selected cases may well respond to antiglucocorticoid therapy. Some preliminary trials in this area would break new ground without sacrificing safety.

Clinical Implications

- Hypercortisolemia is underestimated in maintaining cognitive impairment and psychiatric illness, especially in the elderly.
- Psychiatrists should improve skills in diagnosing HPA axis dysfunction.
- Accurate diagnosis may lead to specific, novel treatments with available antiglucocorticoid strategies.

Limitations

- Evidence is based on research literature review rather than direct research.
- Diagnostic methods for hypercortisolemic treatment resistance are controversial.
- Lack of research in elderly populations leaves the geriatric psychiatrist with only theoretical extrapolations.

References


Résumé

Objectifs : Mettre l’accent sur l’activité de l’axe hypothalamo-hypophysaire surrénalien (HHS), en particulier l’hypercortisolémie endogène, pour en étudier le rôle dans la perpétuation de la maladie psychiatrique et pour considérer la probabilité que les personnes âgées y soient vulnérables.

Méthode : Exposé de cas, analyse de la littérature clinique et de recherche et discussion théorique.

Résultats : Les résultats cliniques et de recherche font largement ressortir que l’hypercortisolémie est toxique pour l’hippocampe. Certaines recherches appuient la position selon laquelle il s’agirait d’un facteur de perpétuation pouvant être traité dans un sous-ensemble de troubles affectifs et de psychoses. Des endocrinologues ont eu recours à des traitements pharmacologiques pour corriger l’hypercortisolémie. Un petit nombre de chercheurs, qui s’intéressent toujours à ce sujet, ont réussi à traiter des psychoses et des troubles affectifs d’étiologie hypercortisolémique en présence ou non de résistance au traitement. Malgré leur pertinence, les données portant sur les psychoses gériatriques sont clairement.

Conclusions : Il nous appartient de mener des recherches sur les méthodes diagnostiques relatives aux psychoses et aux troubles affectifs liés aux états hypercortisolémiques. Très peu de recherches ont été faites sur le sujet, mais nous devons être conscients de la possibilité que les personnes âgées soient plus sensibles à l’endotoxine au cortisol que la population adulte plus jeune. Sans diagnostic précis, nous sommes dans l’impossibilité de tirer parti des stratégies antiglucocorticoïdées actuelles.