BEHAVIORAL DISTURBANCES ASSOCIATED WITH ENDOCRINE DISORDERS

Victor I. Reus, M.D.

Langley Porter Neuropsychiatric Institute, School of Medicine, Department of Psychiatry, University of California, San Francisco, California 94143

ABSTRACT

Patients with major endocrine disorders frequently experience significant changes in mood and mentation. Similarly, many individuals presenting as psychiatric patients have pathologic alterations in neuroendocrine function. Although pathognomic behavioral changes are rare, increased recognition of characteristic symptom complexes may lead to earlier diagnosis and improved treatment planning.

INTRODUCTION

Behavioral symptoms are common in, and in many cases the earliest manifestations of, hormonal disturbance, but the nature of the relationship between neuropsychiatric symptomatology and a given endocrine disorder has historically received inadequate research attention. That this is no longer the case can be attributed to two recent developments. First, in animal and, in some cases, human studies a large number of neuropeptides were found to have specific behavioral effects when administered either centrally or peripherally. This supports the hypothesis that similar phenomena occur endogenously in the pathophysiology of primary disorders of hormonal function (1). Second, the identification of subtle but specific abnormalities in endocrine function in certain psychiatric populations indicates that such patient groups may exist on a continuum with individuals having more severe presentations of endocrine dysfunction. It should be recognized, however, that because of the complex, often
reciprocal relationship between hormonal function and behavioral action, it is premature to attempt to label one set of conditions as “primary” and exerting a causal effect. To this end, certain “primary” endocrine disorders may either arise, or be subject to periodic exacerbation, by change in behavioral circumstance while “primary” psychiatric disorders may either originate, or be significantly shaped by, a “primary” neuroendocrine disturbance (2).

Most of the studies in this review suffer from being retrospective or cross-sectional. The result is that many hormonal disorders seem to exhibit grossly similar behavioral effects, most commonly a depression of mood and initiative and a general impairment of cognition. Longitudinal studies, in which the endocrine dysfunction serves as the independent variable and in which both the biologic and behavioral factors are examined in a covariant fashion over time and treatment, are more likely to provide greater insight into both endocrinologic and psychological function. Additional reviews of characteristic features of individual syndromes can be found in the recent literature (3–5).

CUSHING’S SYNDROME

In his original observations, Cushing noted that patients with the syndrome frequently showed changes in cognitive and affective state. Most systematic investigations since report evidence for psychiatric disturbance in over 50% of patients studied, with psychosis and/or suicidal ideation or action evident in over 10% of patients (6–8). Interestingly, in several studies a major emotional disturbance appeared to precede the onset of somatic symptomatology (9). There is some evidence that the character of the mood disorder varies with stage of illness; reports and observations of euphoria and increased motor activity are common early on in the course, and chronic symptoms of depression, irritability, disturbed concentration and memory, and anxiety occur later.

Cognitive impairment is most notable in nonverbal visual ideational and visual memory functions (10). Usually appearing in consort with somatic changes, the changes in mood and cognition can in certain circumstances appear independently as the most prominent presenting features of the syndrome. Particularly in individuals with intermittent or “transient” Cushing’s syndrome, the somatic pathology may be evanescent and mild in comparison to the mood disturbance. A causal association between endocrine and behavioral disturbance is supported by data indicating that reductions in cortisol level and output following clinical intervention usually result in markedly improved mental states (11). In one published case, metyrapone rapidly alleviated the neuropsychiatric manifestations of
Cushing's syndrome. This suggests that hypercortisolism caused the depression, sleep disturbance, and inappropriate behavior (12).

Individuals presenting with the classic stigmata of the disorder seldom present a diagnostic dilemma. However, it has become clear from systematic investigations that most of the salient signs of the disorder, such as obesity, hypertension, hypertrichosis, and osteoporosis, are neither inevitably found in nor specific to individuals who otherwise meet laboratory requirements for the diagnosis of Cushing's syndrome (13). Because many patients with severe depression have associated abnormalities in hypothalamic-pituitary-adrenal function, it is not always possible to discriminate the "psychiatric" patient presenting with such signs from a patient with mild or "transient" Cushing's syndrome. Several authors have reported that cortisol response to insulin-induced hypoglycemia and to high-dose dexamethasone administration might be employed successfully in the differential diagnosis (14). These suggestions, however, do not address other data that indicate that abnormal responses on these assessments can occur in patients believed to have a "primary" psychiatric disorder (15).

ADDISON'S DISEASE

Despite their physiologic differences, the psychiatric presentation of Addison's disease may be similar to that of Cushing's syndrome. Presenting symptoms include apathy, social withdrawal, fatigue, anhedonia, poverty of thought, and negativism. A true organic psychosis can also occur, characterized by cognitive impairment and confusion, and in certain cases stupor or coma. The relationship of these symptoms to decreased levels of glucocorticoids is clear in that there is a quick resolution with glucocorticoid replacement. Correction of the electrolyte imbalance does not by itself result in observable benefit. If psychiatric symptomatology is profound and antedates the more classic somatic features, misdiagnosis may occur. In a recent case report, such a patient was initially diagnosed as suffering from bereavement and conversion disorder after having presented with a history of weakness, shortness of breath, and a three-week period of crying, decreased concentration, impaired sleep, nausea, decreased appetite, and apathy (16).

Specific changes in sensory function and sleep regulation have also been reported. In general, in the absence of glucocorticoids, sensory detection acuity is enhanced, while "integration" of sensory input and recognition appears decreased. The visual evoked response of Addison's patients is of small amplitude and short latency at baseline and increases with replacement glucocorticoid. Whether such alterations in physiologic and be-
havioral response should be attributed directly to the adrenal cortical deficiency itself or to the compensatory increases in corticotropin and corticotropin-releasing factor is at present unclear; evidence is accumulating that the latter compounds exert specific effects on a variety of attentional and affective processes.

HYPERPARATHYROIDISM

Hyperparathyroidism is commonly associated with a panoply of subtle changes in affect and cognition. Generalized fatigue, an absence of initiative and spontaneity, depression, reduced concentration, memory impairment, and occasionally, irritability and paranoia are the most characteristic features (17, 18). In some cases, an organic psychosis develops, associated with true disorientation, delirium, hallucinations, and confusion. Such changes usually develop over a course of several years and appear to be generally, although not invariably, related to the degree of hypercalcemia noted. The individual variation is great, however, and patients with prominent changes in calcium level may have no observable behavioral alteration.

Assessments of the neuropsychological deficit associated with primary hyperparathyroidism indicate that dominant hemispheric functions such as verbal memory and logic are most likely to be adversely affected (19). Surgical removal of the parathyroid adenoma in cases of primary hyperparathyroidism (and reduction of serum calcium in syndromes of other etiology) usually results in dramatically improved neuropsychological function and resolution of the affective disturbance. Clinicians should be aware, however, that post-parathyroidectomy psychosis has also been recorded, ostensibly related to the rapid decrease in serum calcium (20). The differential diagnosis of hyperparathyroidism and hypercalcemia includes treatment with lithium carbonate. Lithium administration can increase parathormone and calcium blood levels. In rare cases, this leads to the discovery of a parathyroid adenoma; it is not clear whether this represents a coincidental finding.

HYPERTHYROIDISM

Psychopathology in thyrotoxic patients has been recognized since the early 1800s, the clinical picture being that of an acute confusional state or an activated mood disorder, similar to mania. Less severe behavioral changes include increased anxiety, hyperactivity, irritability, and emotional lability (21–23). Atypical presentations consisting of psychomotor retardation and apathy have been described in rare cases. Isolated hyperthyroxinemia, such
as occurs in "euthyroid sick" syndrome, may be associated with similar symptomatology in the absence of tissue evidence of thyrotoxicosis (24, 25). Surveys of large numbers of unselected psychiatric patients indicate that levels of serum thyroxine are frequently elevated, although detailed correlations with specific behavioral symptom clusters have not been reported. In certain cases, euthyroid hyperthyroxinemia has preceded the onset of recurrent manic episodes (26). There is some evidence that hyperthyroidism is uniquely associated with the development of a phobic disorder in a subgroup of patients and that a reduced TSH response to TRH occurs more frequently in patients with a past history of violent suicidal behavior than in matched controls (27, 28).

The impairment in cognitive function in hyperthyroidism is generally milder than that observed in hypothyroidism. Whybrow et al (29) presented objective validation of subjective complaints of diminished recent memory (principally impaired retrieval) and decreased span of attention. These disruptions in cognition resolve when thyroid function is normalized.

Starting with a report by Perry in 1825 and with subsequent observations by Graves himself in 1835, clinicians have recognized that acute thyroid dysfunction, in some cases complete with goiter, can be precipitated by severe psychic stress. Thyroid "hot spots" may disappear during periods of minimal stress, and may enlarge and result in clinical hyperthyroidism during periods of prolonged, severe stress (30). Such activation of thyroid dysfunction by emotional circumstance probably occurs in a clinically meaningful sense only in individuals who have an underlying endocrinologic vulnerability, such as "painless" or "silent" thyroiditis.

HYPOTHYROIDISM

The behavioral changes associated with long-standing hypothyroidism are classic and seldom misdiagnosed in the current environment of routine thyroid screening. Signs of fatigue, decreased libido, memory impairment, and disruption of sleep pattern are most characteristic (31–33). In severe or long-standing cases, patients may present with a true organic psychosis, characterized frequently by paranoid delusions, or cortical dementia.

It is now recognized that thyroid dysfunction is not an "all-or-none" phenomenon but exists over a continuum. Individuals with "subclinical hypothyroidism" whose peripheral hormone levels are within the normal range and who lack the classic physical features may nonetheless suffer marked impairment in emotional and psychological spheres. In patients whose peripheral thyroxine, triiodothyronine, and thyroid-stimulating hormone levels fall within the normal range, the evaluation of TSH response to thyrotropin-releasing hormone (TRH) is necessary to arrive at
the proper diagnosis. Increasing utilization of this test of pituitary reserve in psychiatric diagnosis has revealed that many patients routinely referred for evaluation and treatment of a "primary" depression have in fact subclinical hypothyroidism (34–36). Such individuals show a lesser therapeutic response to mood-altering agents like tricyclic antidepressants and lithium carbonate and may develop rapid mood cycling in the course of treatment with these agents. Thyroid replacement generally improves emotional state and mental functioning. When thyroid replacement is administered either too quickly or at too high a dose, however, an activated manic-like state can be precipitated (37). The syndrome is characterized by increased physical activity, persecutory delusions, an elevated irritable mood, poor judgment, and anxiety. It lasts from one to two weeks and resolves without sequelae.

The effects of increased or decreased hormonal level on brain function are different at different stages in life. Deficiency of thyroid hormone at critical stages of brain development results in aberrant maturation of the cerebral and cerebellar cortex and the clinical syndrome of cretinism. Subclinical deficits in motor and cognitive performance measured 10 to 12 years after birth in the absence of cretinism have been correlated with maternal thyroid function (38). The mechanism by which thyroid hormone modulates mood and cognitive function is speculative, but mediation of beta-adrenergic receptor response is a prime candidate (39).

Although the cause of primary hypothyroidism is in most cases unknown, the identification of antithyroid antibodies in many patients indicates an autoimmune etiology (40, 41). Autoimmune thyroiditis not associated with clinical hypothyroidism, i.e. "symptomless," "silent," or "transient" thyroiditis, may nonetheless be characterized by behavioral pathology. An admixture of both hyper- and hypothyroid symptoms can occur even when the patient is euthyroid by laboratory examination. This condition is thought to represent an early stage of chronic lymphocytic thyroiditis and either progresses to true hypothyroidism or is characterized by recurrent periods of symptomatic remission. Several recent studies would indicate that 10 to 20% of female patients with "primary" depressive diagnoses meet the criteria for autoimmune thyroiditis and are not "symptomless" at all in terms of behavioral function.

In early stages of the syndrome patients will usually experience recurrent fluctuations in mood state, with short periods of fatigue and anergic depression punctuated by periods of increased energy and mood. As the disorder progresses these patients complain of profound mental and physical sluggishness and a complex of somatic complaints, including headaches, food allergies, gastrointestinal distress, menstrual irregularities, decreased libido, and weight gain. Because of the variety of multisystem complaints and findings of euthyroidism on laboratory examination, these
patients are often formally diagnosed as having somatization disorder or hysteria. Specific complaints of "being in a fog," or of one's head seeming "full of cotton or wool," and histories of suicidal ideation or action are characteristic.

Autoimmune thyroiditis is a common cause of thyroid disease in children and is associated with severe behavioral pathology in a subgroup of individuals. The prevalence of transient hypothyroidism and autoimmune thyroid dysfunction in the postpartum period is quite high, occurring in as many as 10% of women studied (42, 43). Increased complaints of anxiety and depression in the months following delivery have been reported. In view of these data and clinical reports of an increased incidence of postpartum depression in women with chronic lymphocytic thyroiditis, it would appear that the existence or development of antithyroid antibodies in the postpartum period increases the risk of depressive symptomatology.

Even when laboratory data indicate an apparent euthyroid state, patients with autoimmune thyroiditis will usually report modest to dramatic improvement with thyroid augmentation. Such individuals are sensitive to small doses of thyroid hormone but chronic changes in mentation, mood, and personality often only after months of treatment. Adjunctive treatment with beta blockers and benzodiazepines is also useful, particularly with symptoms of anxiety, restlessness, and sleep disturbance. In a small but significant percentage of cases, thyroid augmentation is of inadequate benefit and antithyroid antibody titers persist despite maximal replacement. There is some clinical evidence that such patients respond beneficially to surgical intervention but this remains a controversial procedure.

HYPERPROLACTINEMIA

Prolactinomas account for approximately 60% of all primary pituitary tumors and are commonly associated with symptoms of apathy and decreased libido, as well as visual disturbance, genital dysfunction, and headache (44–46). Prominent irritability and impulsiveness are also sometimes noted. Despite these observations, the relationship of a change in prolactin level to alteration in behavior is still obscure. Although dramatic resolution of behavioral symptomatology may occur with surgical or drug treatment, some patients with extremely elevated prolactin levels will present with no alteration of mental state. In those patients in whom behavioral changes are noted, apathy rather than depression per se seems characteristic. Such patients are less likely to express their internal sense of distress and may not meet formal diagnostic criteria for a major affective disorder.
HYPOPITUITARISM

It is difficult to encompass the full range of adverse behavioral symptoms that can result from partial or complete destruction of pituitary architecture. Primary tumors, idiopathic states, or necrosis can produce a composite of signs and symptoms attributable to loss of individual target gland hormones (47). Overall, patients with hypopituitarism commonly become dependent, drowsy, irritable, negativistic, and seem to lose their drive and initiative. Confusion and true delusions also occur. In cases of hypogonadotropic hypogonadism, decreased libido and aggressiveness are salient features. In general, replacement therapy will improve some dimensions but not others. Chronic fatigue, lack of initiative, and memory impairment are the most resistant to treatment. Why this should be is unclear although specific behavioral roles for growth hormone and prolactin deficiency have been suggested.

Literature Cited


