Late-Onset Congenital Adrenal Hyperplasia: A Treatable Cause of Anxiety

Alan R. Jacobs, Phyllis B. Edelheit, Anton E. Coleman, and Andrew G. Herzog

Background: Some intermediaries of cortisol synthesis, especially the sulfated ester of dehydroepiandrosterone (DHEAS), are picrotoxin-like antagonists of the γ-aminobutyric acid A (GABA-A) receptor and exert potent anxiogenic effects. We report 5 men and 7 women with refractory anxiety disorders, who had late-onset congenital adrenal hyperplasia (CAH), and in whom interactions between neuroactive steroids and anomalous brain substrates may have participated in the pathophysiology and treatment of anxiety.

Methods: Twelve patients with refractory anxiety disorders as defined by DSM-IV had elevated DHEAS and specific enzyme deficiencies diagnostic of CAH. All were treated with adrenal suppressive therapy using ketoconazole or low (physiologic) dose glucocorticoids. Anxiety was rated by the Tension Scale of the Profile of Mood States (POMS Tension) questionnaire before and during hormonal treatment.

Results: Reduction of DHEAS was associated with lower anxiety scores in all twelve cases. POMS Tension scores decreased by 55%. Hormonal treatment, which failed to lower DHEAS, was ineffective.

Conclusions: These findings suggest that late onset CAH can contribute to anxiety disorders and that adrenal suppressive therapy or inhibition of steroidogenesis with ketoconazole may be efficacious as adjuvant therapy.

Key Words: Anxiety, dehydroepiandrosterone sulfate, adrenal, behavior, hormones

Introduction

Late-onset congenital adrenal hyperplasia (CAH) is an autosomal recessive adrenocortical disorder that occurs in approximately 1% of the general population and is characterized by partial deficiency of steroidogenic enzymes essential for cortisol biosynthesis (Eldar-Geva et al 1990; Miller 1991). CAH is most commonly due to an enzyme deficiency of 21-hydroxylase, 11β-hydroxylase or 3β-oxidoreductase, alone or in combination (Eldar-Geva et al 1990; Miller 1991). In women, CAH can cause hirsutism, menstrual disorders, and infertility (Eldar-Geva et al 1990; Miller 1991). In men, distinguishing physical features are generally absent. While the coexistence of mood disorder and CAH has been described (Feldman et al 1987), a possible role for CAH in anxiety disorders has not been previously reported.

There is reason to consider a pathophysiologic role for CAH in anxiety disorders. CAH can cause the accumulation of intermediaries in the adrenal steroid hormone synthetic pathways. Some of these compounds, especially dehydroepiandrosterone sulfate (DHEAS) and pregnenolone sulfate, are neurosteroids that have potent activity as antagonists at the γ-aminobutyric acid-A (GABA-A) receptor in the brain. They can exert potent anxiogenic, proconvulsant, and convulsant effects (Deutsch et al 1992; Paul and Purdy 1992). Excitatory neurosteroids may be more apt to cause emotional disorders in individuals with anomalous brain substrates than in those who have not inherited or acquired any degree of cerebral dysfunction (Brooks-Kayal et al 1998a; 1998b; Geschwind et al 1985; Herzog 1989; Schmidt et al 1998). We report 5 men and 7 women with refractory anxiety disorders who were demonstrated to have CAH and whose anxiety decreased during treatment of their CAH.

Methods and Materials

The men and women ranged in age from 16 to 55 years and were diagnosed by psychiatrists or behavioral neurologists to have an anxiety disorder as defined by DSM-IV criteria. Anxiety, in all cases, was considered refractory to psychotropic medications (protracted trials of benzodiazepines, antidepressants, mood stabilizers, and/or major tranquilizers) because of inadequate efficacy or intolerable side effects. The anxiety disorders included generalized anxiety, panic disorder, phobias, and obsessive-compulsive disorder. Some also suffered from depressive or bipolar forms of major mood disorder. Ten of the twelve had some evidence, by history, examination, or laboratory (neuropsychologic, electroencephalographic, or brain imaging) investigations, of forebrain anomaly. All patients were found to have elevated levels of DHEAS and subsequently were shown to have...
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<th>Pt</th>
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<th>Age</th>
<th>Hand</th>
<th>Medications</th>
<th>Clinical Response</th>
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Anxiety disorders: A, 300.02 generalized anxiety disorder; P, 300.01 panic disorder without agoraphobia; Ph, 300.29 specific phobia, situational type; OCD, 300.3 obsessive-compulsive disorder.
Mood/Psychosis: D, 296.3x major depressive disorder, recurrent; B, 296.7 bipolar I disorder, most recent episode unspecified; P, 298.9 psychotic disorder not otherwise specified.
Neurologic signs: H, hemispheric signs.
Neuropsychological signs: I, global intellectual impairment; A, attentional deficit; M, memory deficit; L, language deficit; V, visuospatial deficit.
Congenital adrenal hyperplasia (CAH) type: 21-OH, 21 hydroxylase deficiency; 11-β-OH, 11β-hydroxylase deficiency; 3-β-OR, 3-β-oxidoreductase deficiency.
Medications: keto, ketoconazole; pred, prednisone; dex, dexamethasone; cort, hydrocortisone.

Table 1. Demographic, Historical, Clinical and Laboratory Data for 12 Patients with Refractory Anxiety Disorders and CAH Whose Anxiety Decreased with Adrenal Suppressive Therapy.
specific enzyme deficiencies diagnostic of CAH (Eldar-Geva et al 1990). Table 1 provides details of demographic, historical, clinical, and laboratory data for the 12 patients.

Adrenal suppressive therapy was added to existing treatment regimens in all 12 cases. Treatment duration at the time of this report ranged between 3 to 16 months. Ketoconazole was considered the therapy of choice because low doses selectively inhibit C17,20-lyase, the enzyme directly responsible for the conversion of 17-hydroxypregnenolone to dehydroepiandrosterone (Couch et al 1987; Holland et al 1985; Sonino 1987). Glucocorticoid treatment was used for suppression when normalization of DHEAS could not be achieved with ketoconazole (patients 1, 7, and 12). Table 1 presents the specific regimens and results of treatment.

Anxiety was rated by the Tension score of the Profile of Mood States (POMS) (McNair et al 1992) questionnaire. All 12 patients completed pre- and post-treatment POMS questionnaires. All attempts were made to keep constant the doses of any concomitant psychoactive medications during the period of treatment with adrenal suppressive medication.

### Results

Adrenal suppressive therapy was associated with a reduction of anxiety in all 12 patients (p < .001, nonparametric sign test). The POMS tension scores were reduced by an average of 55% (range: 31–89%; p = .003, Wilcoxon signed rank test). In contrast, the POMS depression scores showed inconsistent directional changes.

A favorable clinical response was associated with normalization or substantial reduction (greater than 10%) of DHEAS levels using ketoconazole in 8 patients. Patients 1, 7, 10, and 12 did not achieve substantial lowering of DHEAS levels on ketoconazole, but did so with glucocorticoids. Clinical improvement in these cases was associated with the latter therapy only.

### Discussion

We report 5 men and 7 women with refractory anxiety who were demonstrated to have CAH and responded favorably to reduction of serum DHEAS levels. There are reasons to consider that the response to therapy represents more than a placebo effect. Anxiety in all of the patients in the series was considered refractory to psychotropic medications because of inadequate efficacy or intolerable side effects. The favorable responses were specific for anxiety disorders, not mood disorders, and persisted for extended durations (currently, 16 months in patient 11). Finally, clinical improvement appeared to relate to endocrine correction, as demonstrated by lowering of DHEAS. Another possibility is that ketoconazole has sedative effects unrelated to its actions on steroidogenic enzymes. In patients 1, 7, 10, and 12, however, this is not the case since these patients did not respond to ketoconazole treatment, which was not accompanied by significant reduction of DHEAS, but did respond favorably to glucocorticoids, which successfully lowered DHEAS levels.

We speculate that alterations in the plasma concentrations of anxiogenic and anxiolytic neuroactive adrenal steroids may be important in the development and treatment of anxiety disorders associated with CAH. Some major metabolites of progesterone and deoxycorticosterone act at the GABA-A receptor as positive allosteric effectors with anxiolytic, sedative-hypnotic, and anticonvulsant properties, while other intermediaries such as DHEAS and pregnenolone-sulfate have been shown to be potent GABA-A receptor antagonists with anxiogenic, proconvulsant, and convulsant properties (Deutsch et al 1992; Paul and Purdy 1992). Lowering DHEAS levels or raising progesterone metabolite levels, therefore, should theoretically reduce anxiety disorders. This possibility is supported by endocrine data in patient 4 (Table 2). At low doses, ketoconazole primarily inhibits 17,20-lyase, which directly blocks the conversion of 17-hydroxypregnenolone to dehydroepiandrosterone. In patient 4, this led to a decrease in all excitatory neuroactive hormones (DHEAS, 17-hydroxypregnenolone, and estradiol) and an increase in all the inhibitory neurosteroids (deoxycorticosterone, 17-hydroxyprogesterone, and progesterone) (Deutsch et al 1992; Paul and Purdy 1992). These changes were associated with a marked reduction in anxiety (POMS decreased 41%). Higher dose ketoconazole begins to also inhibit 11-B-hydroxylase, which blocks cortisol synthesis, thus increasing ACTH response and increasing global adrenal steroid synthesis (Deutsch et al 1992; Paul and Purdy 1992). This led to increases in all measured steroids,
excitatory and inhibitory, and a moderate return of anxiety (POMS increased 50%).

The findings raise the possibility that the elevation of excitatory neuroactive steroids, either in absolute terms or relative to inhibitory steroids, may be an important and treatable factor in the development of anxiety disorders in men and women with CAH, especially in the setting of anomalous brain substrates. DHEAS may be a suitable screen for CAH in the majority of cases. Some individuals with CAH (e.g., those with 3β-oxidoreductase deficiency), however, may have normal DHEAS levels and require screening of other intermediaries (e.g., androstenedione, DHEA, or 17-hydroxyprogesterone). At present, the most sensitive evaluation remains the 1,24-adrenocorticotropin stimulation test (Eldar-Geva et al 1990).

References


