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Research report

Defining the boundaries of atypical depression: Evidence from the HPA axis supports course of illness distinctions

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Abstract

Background: Treatment outcome and brain laterality differ between early onset (<20 years) chronically (no well-being >2 months) depressed patients with atypical features (early/chronic atypical) and those with either later onset or less chronic illness (late/nonchronic atypical). Because hypothalamic–pituitary–adrenal (HPA) axis abnormalities have been hypothesized to distinguish atypical depression from melancholia, we examined whether HPA measures would also differentiate these two groups of depressed patients with atypical features.
Methods: Three-hour afternoon cortisol levels, stimulation of cortisol by afternoon dextroamphetamine, and suppression of cortisol by dexamethasone were investigated in 85 depressed patients with atypical features. The latter group was divided into early/chronic atypical and late/nonchronic atypical based on chart review of course of illness.
Results: Patients with early/chronic atypical had significantly lower mean 3 h afternoon cortisol levels (N=21) and 4:00 p.m. post-dexamethasone cortisol levels (N=20) than did those with late/nonchronic atypical (N=43 with afternoon cortisol; N=26 with post-dexamethasone cortisol). Post-dextroamphetamine cortisol levels were numerically higher in the early/chronic atypical group (N=15 vs. 19), but this failed to reach conventional significance ($0.05<p<0.1$). Arbitrary categorical distinctions of normal and abnormal did not separate these groups on any of the tests.
Limitations: Lack of demonstrated reliability of the chart review and retrospective determination of atypical features and course of illness limit the generalizability of these findings.
Conclusions: These HPA data are consistent with earlier treatment and brain laterality findings that course of illness distinguishes biologically distinct groups within depressed patients with atypical features. The DSM should consider adding course of illness requirements to its criteria for atypical features.

Keywords: Atypical depression; HPA axis; Age of onset; Chronic

Based on treatment outcome, longitudinal course, biologic and physiologic data, and family histories (Rabkin et al., 1996), the American Psychiatric Asso-

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ciation's Diagnostic and Statistical Manual, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) added atypical features as a parenthetical modifier of major depression and dysthymia. Several recent reports suggest that DSM-IV criteria for depression with atypical features identify a heterogeneous group distinguishable by course of illness. Those having both early onset (i.e., before age 20 years) and a very chronic illness (i.e., no spontaneous well-being since onset greater than 2 months) (early/chronic atypical) are no more likely to benefit from tricyclic antidepressant than from placebo (Stewart et al., 2002), but do respond to a monoamine oxidase inhibitor, and do not have increased left hemisphere perceptual processing (Stewart et al., 2003). In contrast, similar patients who report either later onset or a less chronic course of illness (late/nonchronic atypical) respond robustly to tricyclic antidepressant (Stewart et al., 2002), and show evidence of increased left hemispheric processing (Stewart et al., 2003). Because both tricyclic responsivity (Bielski and Friedel, 1976; Joyce and Paykel, 1989) and increased left hemisphere processing (Bruder et al., 1989) are characteristic of patients with melancholia, the patients with late/nonchronic atypical appear to resemble depressed patients with melancholic features more than they do patients with early/chronic atypical.

Endogenously depressed patients have a variety of hypothalamic–pituitary–adrenal (HPA) axis abnormalities, including hypersecretion of cortisol, relative nonsuppression of cortisol following dexamethasone, and relative lack of cortisol response following dextroamphetamine stimulation (e.g., Sachar et al., 1985). Because patients with late/nonchronic atypical were more similar to patients with melancholia in their tricyclic response and perceptual processing, we hypothesized that like depressed patients with melancholic features, the late/nonchronic atypical patients would have elevated afternoon cortisol and post-dexamethasone cortisol, and blunted post-dextroamphetamine cortisol relative to those with early/chronic atypical.

1. Methods

One hundred and sixty depressed patients took part in HPA testing between 1978 and 1981. All had been diagnosed according to RDC (Spitzer et al., 1978) based on SADS (Endicott and Spitzer, 1978) interview. Charts were reviewed blind to HPA results to determine whether patients met DSM-IV criteria from depression with atypical features, as well as age of onset of first significant dysphoria (not necessarily first major depressive episode) and whether subsequent illness included one or more episode of spontaneous well-being. Eighty-five were found to meet these criteria and are the subjects of this report. As in the two prior reports (Stewart et al., 2002, 2003), onset was divided at age 20 and chronic illness was defined as at least 2 years duration plus no spontaneous well-being lasting as long as 2 months since onset.

1.1. HPA tests

1.1.1. Three-hour afternoon cortisol

Patients arrived at approximately 11:00 a.m., had a heparinized catheter placed in an antecubital vein by 11:30 a.m. Beginning at 1:00 p.m., blood was withdrawn every half hour until 4:00 p.m. (i.e., seven samples).

1.1.2. Dexamethasone suppression (DST)

Patients were given dexamethasone 1 mg to be taken at 11 p.m. The next day, blood was drawn at 4:00 p.m.

1.1.3. Dextroamphetamine stimulation

Some patients had this test immediately following their 3-h cortisol collection, the 3:30 and 4:00 p.m. bloods being used for baseline cortisol determination for the dextroamphetamine test. Patients who did not have the 3-h cortisol collection or had it on a different day had a heparinized catheter inserted into an antecubital vein by 3:00 p.m. Blood was then withdrawn at 3:30 and 4:00 p.m. for pre-dextroamphetamine cortisol determination. Immediately following the 4:00 p.m. blood withdrawal, dextroamphetamine 0.15 mg/kg was injected intravenously over 45 s. Blood was then withdrawn every 15 min for 90 min.

When patients participated in more than one test, the 3-h cortisol collection always preceded the challenge tests, and the DST and dextroamphetamine tests were separated by at least 2 days.