Longitudinal Course of Adolescent Depression: Neuroendocrine and Psychosocial Predictors

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Objective: The study examined whether cortisol measures are associated with the clinical course of depression in adolescents. Furthermore, the study evaluated whether the relationship between cortisol and clinical course is moderated by environmental stress and/or social support. **Method:** Fifty-five adolescents with depression (age range 13–18 years) were recruited. In addition to a systematic diagnostic assessment, information was obtained on environmental stress and social support. Urinary free cortisol measures were collected on three consecutive nights during the index episode. Clinical follow-up evaluations were conducted at regular intervals over a 5-year period, documenting recovery from the index depressive episode and recurrent episodes. Information on environmental stress and social support also was gathered during each follow-up assessment. **Results:** Consistent with prior reports, the majority of adolescents (92.2%) recovered from the initial depressive episode. A substantial proportion of the recovered youth (42.6%) experienced a subsequent episode during the follow-up period. Higher cortisol levels were associated with a longer time to recovery from the index depressive episode. The effect of cortisol on recovery was moderated by social support. The combination of elevated cortisol and recent stressful experiences predicted recurrence, whereas a higher level of social support was protective against recurrence. **Conclusions:** These data, in conjunction with prior literature, suggest that depression reflects an underlying neurobiological vulnerability that may predispose individuals with high vulnerability to chronic, recurrent episodes. Psychosocial factors, independently or in combination with an underlying neurobiological vulnerability, also play an important role in determining the clinical course of depression. J. Am. Acad. Child Adolesc. Psychiatry, 2010;49(2): 141–151. **Key Words:** Clinical course, Depression, Hypothalamic–pituitary–adrenal axis, Social support, Stress.

Adolescence is the highest-risk period for development of major depressive disorder.[1] Numerous studies also have documented that early depressive episodes persist or recur into adult life along with ongoing psychosocial difficulties. These difficulties include, but are not limited to, disruption in interpersonal relationships, early pregnancy, low educational attainment, poor occupational functioning and unemployment, as well as increased risk for suicidal behavior, resulting in substantial socioeconomic burden.[2] A better understanding of the factors that predispose youngsters to a chronic, recurrent course will be helpful in the development and implementation of more effective treatment and preventive strategies, thereby allowing such youth to achieve their full potential as adults.[3]

There has been considerable effort to determine the factors associated with the clinical course of depression in youngsters, but it remains unclear which variables exert a potent influence on the course of illness. Among the demographic and clinical variables that were examined, none has been shown yet to consistently predict the clinical course.[2-4] In addition, several psychological and social variables have been proposed as risk factors for chronic and/or recurrent illness, including high neuroticism,

This article is discussed in an editorial by Dr. Neal D. Ryan on page 89.

negative emotionality, negative cognitions, poor social support, and stressful experiences.[2-4]

There is a growing body of research examining neurobiological factors associated with the course of depression in adults. In particular, the hypothalamic–pituitary–adrenal (HPA) system has been studied quite extensively in relation to the pathophysiology and clinical course of depression, based on the theory that the HPA axis mediates/moderates the effects of stress on emotional, cognitive, and behavioral responses.[5,6] For example, a meta-analysis of dexamethasone suppression test (DST) results concluded that although cortisol response to dexamethasone administration does not have a prognostic value during a depressive episode, nonsuppression of cortisol after successful treatment is a robust predictor of relapse in adults.[7] Subsequent studies in recovered patients showed that abnormal cortisol responses to a combination of dexamethasone and corticotropin-releasing hormone (CRH) predicted recurrence.[8,9]

HPA dysregulation also has been linked to pediatric depression.[10] With respect to clinical course, higher cortisol secretion in the evening, a time when the HPA axis is relatively quiescent, predicted persistent depression after 72 weeks.[11] In a separate investigation, higher cortisol secretion near sleep-onset was associated with recurrence.[12] The present work extends these findings by examining the influence of cortisol on recovery and recurrence of depression in the same sample. Measures of environmental stress and social support also were incorporated because stressful experiences have been shown to precipitate depressive episodes both in adolescents and adults, whereas social support has been implicated as a protective factor.[2-4]

To the best of our knowledge, this is the first study to use HPA, stress, and social support measures simultaneously in relation to the clinical course of adolescent depression. The following hypotheses were postulated: 1) adolescents with lower cortisol levels (measured at recruitment) would recover faster from the index depressive episode compared with their counterparts with higher cortisol levels, 2) the effect of cortisol on recovery from the index depressive episode would be moderated by the magnitude of persistent stress during adolescence, recent stressful life events, and/or social support, 3) among adolescents who recovered from the index depressive episode, those having higher cortisol levels at baseline would be more likely to develop a recurrent depressive episode compared with those with lower cortisol levels, and 4) psychosocial factors would moderate the effect of cortisol on the risk for recurrence.

METHOD

The data reported here are part of a larger study on the development and course of depression in adolescents, as well as the relationship between depression and substance use disorders.[13-15]

Participants

Fifty-five adolescent volunteers with depression were recruited from local mental health and pediatric clinics and schools. The participants met criteria for major depressive disorder, with a minimum duration of 4 weeks and a score of ≥15 on the first 17 items of the Hamilton Depression Rating Scale (HDRS).[16] All participants were between 13 and 18 years, and Tanner stage III, IV, or V of pubertal development.[17,18] Exclusionary criteria included current or prior history of mania/hypomania, psychotic disorder or substance use disorder symptoms, and family history of bipolar disorder. Participants were free of psychotropic agents for at least 8 weeks, and were medically healthy and free from alcohol or illicit drug use as confirmed by laboratory investigations and a urine screen. Other exclusionary criteria included weight greater than 150% of ideal body weight for age and gender, and weight or height less than one-third percentile. Before performing the research procedures, all adolescent participants signed a written assent form and parents signed an informed consent document, approved by the local Institutional Review Boards.

Diagnostic Evaluation

Diagnoses were based on a semi-structured interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children—the Present and Lifetime Version (K-SADS-PL).[19] Interrater and test–retest reliability have been established for K-SADS-PL, as well as convergent and discriminant validity.[19] The K-SADS-PL was administered separately to the adolescent and parent, and summary scores were tabulated. HDRS, Children's Global Assessment Scale (CGAS),[20] Beck Depression Inventory (BDI),[21] and Hollingshead Socioeconomic Scale[22] also were completed.

The Family History-Research Diagnostic Criteria (FH-RDC), a semi-structured interview, was used for the evaluation of psychiatric disorders in family members.[23] A parent was interviewed regarding lifetime psychiatric disorders in all first-degree relatives of the adolescent subject (including the self, spouse, and all