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Research report

Childhood anxiety: An early predictor of mood disorders in offspring of bipolar parents

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ABSTRACT

Background: Anxiety disorders are common among the offspring of parents with bipolar disorder (BD). This study investigated the nature of the association between anxiety disorders and mood disorders in a prospectively studied high-risk cohort.
Methods: High-risk offspring were identified from families in which one parent had confirmed BD based on SADS-L interviews and best estimate diagnostic procedures. All agreeable offspring aged 8–25 years were enrolled in a longitudinal study involving repeated KSADS-PL format clinical assessments. Control (C) offspring from families in which neither parent met lifetime criteria for a psychiatric disorder were similarly assessed. All DSM-IV diagnoses in the offspring were confirmed on blind consensus review. Cumulative incidence and adjusted Cox Proportional Hazards models were used to calculate the risk of anxiety disorders and the predictive association with mood disorders.
Results: The cumulative incidence of anxiety disorders was higher (23.40% vs. 10.42%; HR=2.136; $p=.0382$) and occurred earlier (9.79 vs. 14.84 years; $p=.0125$) in high-risk compared to C offspring. In high-risk offspring generalized anxiety disorders (GAD) followed by social phobia were the most incident anxiety subtypes; while high emotionality (HR 1.111; $p=.0096$) and shyness (HR 1.144; $p=.0053$) increased the risk of anxiety disorders. Anxiety disorders increased the adjusted risk of mood disorders (HR 2.166; $p=.0004$), on average 8.49 years later (SD 5.97).
Limitations: The cumulative incidence of BD is relatively low, as the cohort is still in the period of risk.
Conclusions: Findings highlight the need for longitudinal surveillance of symptomatic high-risk children and suggest anxiety disorders are an important early intervention target.

1. Introduction

Anxiety disorders are the most common psychiatric disorders diagnosed in children (Merikangas et al., 2010), and can persist into adulthood either solely or in combination with other anxiety or non-anxiety psychiatric illnesses (Kim-Cohen et al., 2003). In individuals with bipolar disorder (BD), anxiety disorders are a particularly common comorbidity (Magalhaes et al., 2012; Merikangas et al., 2011; Sala et al., 2012). To wit, recent findings from the World Mental Health Survey Initiative reported comorbid anxiety disorders in 62.9% of adults with BD (Merikangas et al., 2011). Consistent with this, the Systematic Treatment Enhancement Program for Bipolar Disorder (Perlis et al., 2004) reported anxiety disorders as the most frequent comorbidity compared to other major DSM Axis I disorders in patients with BD, with a particularly high prevalence of anxiety disorders amongst early onset patients (69.2%). Comorbid anxiety disorders in adults with BD are associated with poorer clinical outcomes, worsened psychosocial functioning and specific socio-demographic factors (Henry et al., 2003; Magalhaes et al., 2012; McIntyre et al., 2006; Sala et al., 2012).

Despite the strength of the association between BD and anxiety disorders, there is limited understanding as to the origins of this association. BD is highly heritable (McGuffin et al., 2010), with adolescence marking the beginning of the risk period for the onset of bipolar-related mood episodes (Duffy et al., 2009). Therefore, longitudinal prospective studies of the offspring of BD parents are

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informative as to the nature of the relationship between BD and anxiety disorders. Recent findings from independent high-risk studies suggest that anxiety disorders may be reliable antecedents to subsequent mood disorders in this population (Duffy, 2010; Nurnberger et al., 2011). In an earlier analysis, unadjusted for sibling correlation and other confounds, we reported that major mood disorders were 2.6 times more likely to develop in those high-risk offspring with compared to those without a childhood anxiety disorder (Duffy et al., 2010). Moreover, anxiety disorders were not simply a prodrome to or an early symptom of an impending mood episode, but rather manifest as distal childhood antecedents.

Since the preliminary observations of the association between childhood anxiety and subsequent mood disorders, continued longitudinal observations have led us to propose a clinical staging model describing the development of bipolar and related mood disorders in youth at confirmed genetic risk (Duffy et al., 2010). In this model anxiety disorders represent one of the most robust early clinical predictors of the subsequent progression of full-blown BD. This suggests that in children at confirmed genetic risk for BD, anxiety disorders have important prognostic implications for the subsequent development of bipolar-related mood disorders in adolescence and early adulthood.

Here we present new findings from a new analysis of anxiety disorders in a large dynamic (following existing and adding new) cohort of offspring from well-characterized families observed for up to 16 years. Given that the proband parents were themselves studied prospectively and treated systematically in accordance with research protocol, we were able limit inclusion to families in which one parent had confirmed BD determined to be either responsive or non-responsive to long-term lithium prophylaxis (Grof et al., 1994, 2009; Grof, 2010). Excellent response to lithium prophylaxis identifies a relatively homogeneous subtype of BD with characteristic neurobiological correlates.

Specific aims of this analysis adjusted for potential confounds of variable length of observation, sex, SES and sibling correlation, included: (i) to describe the cumulative incidence of anxiety disorders in high-risk compared to control offspring, (ii) to identify predictors of anxiety disorders in high-risk offspring and (iii) to determine the association between antecedent anxiety disorders and subsequent mood disorders in high-risk offspring.

2. Methods

2.1. Recruitment of high-risk offspring

The methods of recruitment have been described in detail elsewhere (Duffy et al., 2010). Briefly, all consenting high-risk offspring between the ages of 8–25 years were recruited from families participating in prospective clinical and neurobiological studies. Families were deemed eligible if they had one parent with a DSM-IV lifetime diagnosis of BD and the other parent had no lifetime psychiatric disorder (i.e. major depression, bipolar disorder, psychotic disorder, substance use disorder) on the basis of SADS-L interviews conducted by a psychiatrist and confirmed on blind consensus review by two additional research psychiatrists using all available clinical and research information.

BD parents were treated prospectively by the investigators in specialty clinics providing a wealth of clinical information about the course and treatment response. Published research criteria were used to determine response to lithium prophylaxis (see Turecki et al., 1998 for review). Specifically, after a highly recurrent illness course, those with a clear response to lithium were defined as having no recurrences while on therapeutic lithium (>0.6 mmol/l) for at least three years (LiR); while those with a clear non-response to lithium were defined as having at least two documented recurrences while on therapeutic lithium (LiNR). In 53/229 (23%) of cases, we expanded recruitment within the pedigrees to include the affected first-degree relatives of the BD probands as parents, using the same methods to confirm eligibility. In those parents who had been previously treated prospectively elsewhere, we used a validated scale to determine the lithium response (Garnham et al., 2007).

2.2. Recruitment of control offspring

All consenting control offspring between the ages of 8–25 years were recruited from families identified through two local schools in Ottawa. Following the methods of Goodyeret al., (2000), a demographic screening questionnaire was mailed to families from the school describing the study. Interested families mailed completed questionnaires back to the investigators. Families with children in the age range and in which neither parent indicated a lifetime psychiatric disorder (psychosis, major depression recurrent, substance use disorder) or ongoing serious medical illness (cancer, multiple sclerosis, stroke) were invited to a research interview. Control parents completed SADS-L format clinical research interviews conducted by a psychiatrist and a negative lifetime history of major psychiatric disorders was confirmed on a blind consensus review basis.

2.3. Procedure

As part of this ongoing prospective study, all consenting high-risk and control offspring were clinically assessed on average annually by a research psychiatrist using KSADS-L/SADS-L format interviews (depending on age). All diagnoses were confirmed by two research psychiatrists based on blind consensus review. Sub-threshold symptoms of anxiety, defined as clinically significant symptoms associated with impairment or distress, but not meeting full DSM-IV syndromal criteria, were coded based on consensus review of the clinical interviews and self-report symptom scales including the Hamilton Anxiety Rating Scale (Hamilton, 1959) and the Spence Children's Anxiety Rating Scale (Spence, 1998). Demographic information including age, sex and socioeconomic status (SES) measured by the Hollingshead scale (Hollingshead, 1971) were collected. Psychosocial information including temperament and early adversity were collected using self-report validated scales (see below). This study was approved by local research ethics boards in Halifax and Ottawa.

2.4. Self-report measures

2.4.1. Temperament

The Early Adolescent Temperament Scale (EAS; (Buss and Plomin, 1984)) is a 20-item self-report measure composed of four subscales: emotionality, shyness, activity and sociability. For the purposes of this study only the emotionality and shyness subscales were used. In youth under the age of 13 years a parent-rated version of the EAS was used. The EAS subscales of emotionality and shyness have demonstrated stability over time; for example, 20-month test re-test correlations range between .46–.61 (Mathiesen and Tambs, 1999), and coefficients alpha are typically greater than .75 (Roweet al., 2007).

2.4.2. Early adversity

Childhood abuse was measured using the Childhood Experiences of Care and Abuse Questionnaire (CECA.Q; (Bifulcoet al., 1994)). The CECA.Q is composed of 3 subscales: parental care, physical abuse and sexual abuse. For the purpose of this study only the physical and sexual abuse subscales were used. Abuse was classified as a binary variable (present, not present). The CECA.Q has demonstrated good reliability and validity in community (Bifulco et al., 2005) and clinical samples (Smith et al., 2002).