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Higher risk of developing mood disorders among adolescents with comorbidity of attention deficit hyperactivity disorder and disruptive behavior disorder: A nationwide prospective study

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD) are frequently comorbid. Previous studies suggested that the comorbidity of CD and ODD in ADHD may increase the risk of a further development of mood disorder, but most studies had a small sample size. Using a population-based prospective study design, a large sample composed of 1277 adolescents with ADHD-alone, 46 with ADHD + ODD, 87 with ADHD + CD, and 5640 age/gender-matched controls were enrolled in 2003. These cases were followed to 2010 to identify the cases developing unipolar depressive disorder and bipolar disorder. ADHD + CD groups exhibited a higher prevalence of unipolar depressive disorder (23.0% vs. 13.0% vs. 8.7% vs. 0.7%, $p < 0.001$) and bipolar disorder (3.4% vs. 2.2% vs. 1.3% vs. 0.2%, $p < 0.001$) than ADHD + ODD group, ADHD-alone group, and control group. Adolescents with ADHD + CD, those with ADHD + ODD, and those with ADHD-alone had a higher likelihood of developing unipolar depressive disorder (hazard ratio [HR]: 44.34, 95% confidence interval [CI]: 23.95–71.36; HR: 18.76, 95%CI: 7.87–44.71; HR: 13.01, 95%CI: 8.99–18.82) and bipolar disorder (HR: 14.39, 95%CI: 4.00–51.80; HR: 8.32, 95%CI: 1.06–65.32; HR: 5.24, 95%CI: 2.44–11.24) than the controls. Adolescents with ADHD had elevated risks of unipolar depression and bipolar disorder in their later life, and especially, those with ADHD and comorbidity of CD or ODD exhibited the highest risk. Further study would be required to evaluate whether prompt intervention for ADHD and disruptive behavior problems would decrease the risk of developing mood disorder.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that begins in childhood, and manifests an inability to marshal and sustain attention, and modulate one's activity level and impulsive actions (Biederman, 2005; Biederman and Faraone, 2005; Rappley, 2005). ADHD is highly prevalent in children and adolescents worldwide, affecting approximately 5–7% of children and adolescents, with a male-to-female ratio between 3:1 and 4:1 (Biederman, 2005; Biederman and Faraone, 2005; Rappley, 2005). Children and adolescents with ADHD are frequently comorbid with oppositional defiant disorder (ODD) and conduct disorder (CD), at levels as high as 50% and 15%, respectively (Biederman, 2005; Pliszka, 1998; Smalley et al., 2007; Spencer, 2006). The comorbidity of CD or ODD has great influence on the clinical manifestations of ADHD, leading to the exhibition of a higher severity of inattention and hyperactivity symptoms, more antisocial behaviors, impaired verbal skill, visual motor integration and visuospatial skills, and is related to lower socioeconomic status (August et al., 1983; Connor et al., 2010; Klein et al., 2012; Lahey et al., 1988; Moffitt, 1990; Moffitt and Silva, 1988; Reeves et al., 1987; Shapiro and Garfinkel, 1986).

The association of childhood/adolescent ADHD and adult mood disorder has gained clinical and scientific importance in recent decades (Alpert et al., 1996; McIntyre et al., 2010; Nierenberg et al., 2005; Pliszka, 1998). Some retrospective studies found a substantial proportion of adult patients with mood disorder had childhood/adolescent ADHD. Among 399 adult patients with mood disorder,

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McIntyre et al. also found that 5.4% of patients with major depression and 17.6% of patients with bipolar disorder had the diagnosis of ADHD, and exhibited an earlier age-onset of mood disorder and poorer life quality than those without (McIntyre et al., 2010). Nierenberg et al. assessed the lifetime prevalence of ADHD in 1000 patients with bipolar disorder, and reported that 14.7% of male patients and 5.8% of female patients had lifetime ADHD, and those with ADHD comorbidity had an earlier age-onset of mood disorder, were more frequently depressed, and had a worse course of bipolar disorder (Nierenberg et al., 2005).

Furthermore, several prospective studies suggested that the comorbidity of CD or ODD in ADHD children and adolescents increased the risk of developing mood disorders (Biederman et al., 2003; Biederman et al., 2008a, 2008b; Faraone et al., 1997). A 10-year longitudinal follow-up study investigating the long-term trajectory of CD or ODD comorbidity in ADHD boys showed that ODD was associated with major depression, and CD was associated with a significantly increased risk of psychoactive substance use disorders and bipolar disorder (Biederman et al., 2008a). In a 5-year follow-up study, Biederman et al. found that girls with ADHD + ODD ($n = 37$) at baseline had a significantly increased risk of major depression at the 5-year follow-up compared to those with ADHD-alone ($n = 77$), and both groups of girls with ADHD had an increased risk of bipolar disorder compared to the controls ($n = 107$) (Biederman et al., 2008b). However, these studies were limited by small sample sizes (Biederman et al., 2008a, 2008b).

In this study, using the Taiwan National Health Insurance Research Database (NHIRD) with a prospective 7-year cohort study design and a large sample size, we investigated whether the comorbidity of CD or ODD in adolescents with ADHD would increase the risk of developing unipolar depressive disorder and bipolar disorder in their later life.

1. Methods

1.1. Data source

This study was based on data from the Taiwan NHIRD, one of the biggest medical databases in the world. The database was audited and released by the Taiwan National Health Research Institute. The National Health Insurance (NHI) program was implemented in 1995, and covers up to 99% of all 23,000,000 residents of Taiwan now. Comprehensive information on insured subjects is included in the database, including demographic data, dates of clinical visits, and details of prescriptions. The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan (Chen et al., 2012, 2013; Li et al., 2012).

1.2. Inclusion criteria of patients with ADHD-alone, ADHD + ODD, ADHD + CD, and the control group

Adolescents aged 10–15 years with a diagnosis of ADHD (ICD-9-CM code: 314) given by psychiatrists between January 1, 2003 and December 31, 2003 were included in our study. The enrolled patients were divided into three subgroups: ADHD-alone group, ADHD + ODD (ICD-9-CM code: 313.81) group, and ADHD + CD (ICD-9-CM code: 312) group. Those who had other comorbid psychiatric disorders at enrollment were excluded from our study. The age- and gender-matched control group (4 for every patient in the study cohort) was randomly identified from the subjects after eliminating adolescents who had been given a diagnosis of ADHD anytime and those with any psychiatric disorder before enrollment time. Diagnoses of unipolar depressive disorder (ICD-9-CM codes: 296.2X, 296.3X, 300.4, and 311) and bipolar disorder (ICD-9-CM codes: 296.0X, 296.1X, 296.4X, 296.5X, 296.6X, 296.7X, 296.80, 296.81, 296.89) given by psychiatrists were identified to the end of 2010. The diagnoses were given by psychiatrists according to a diagnostic interview and their clinical judgment. All diagnoses were given at least twice by psychiatrists for diagnostic validity. Level of urbanization based on the post code (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed in our study. The urbanization index (most urbanized region to the most rural region) developed by the National Health Research Institute, Taiwan (Liu et al., 2006).

1.3. Statistical analysis

For between-group comparisons (ADHD + CD vs. ADHD + ODD vs. ADHD-alone vs. control group), the analysis of variance was used for continuous variables and Pearson's X^2 test for nominal variables, where appropriate. Post-hoc analysis with Bonferroni method was performed. Multivariable Cox regression analyses were performed to investigate the hazard ratio (HR) with 95% confident interval (CI) of unipolar depressive disorder and bipolar disorder. A two-tailed P-value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

2. Results

In all, 1410 ADHD adolescents with a mean age of 11.76 ± 1.56 years in 2003 were recruited for our study; they included 1277 patients with ADHD-alone, 46 with ADHD + ODD, and 87 with ADHD + CD. The mean age of ODD diagnosis in patients with ADHD and ODD was 13.90 ± 2.27 years, and the mean age of CD diagnosis in patients with ADHD and CD was 12.01 ± 3.44 years (Table 1). ADHD patients with CD and ADHD patients with ODD had a higher incidence of mood disorders than ADHD-alone and control groups, including unipolar depressive disorder (23.0% vs. 13.0% vs. 8.7% vs. 0.7%, $p < 0.001$) and bipolar disorder (3.4% vs. 2.2% vs. 1.3% vs. 0.2%, $p < 0.001$), during the 7-year follow-up period (Table 1). ADHD + CD group and ADHD + ODD group had the earlier age at onset of unipolar depressive disorder than ADHD-alone group and control group (15.39 ± 2.38 vs. 14.96 ± 2.63 vs. 16.30 ± 2.02 vs. 17.20 ± 2.06 years, $p = 0.005$). Age at onset of bipolar disorder did not differ among four groups ($p = 0.628$). ADHD-alone group, ADHD + ODD group, and ADHD + CD group resided more in northern Taiwan and urbanized region compared to control group (Table 1).

A Kaplan–Meier graph of disease-free survival rates for patients with ADHD-alone, those with ADHD + ODD, those with ADHD + CD, and the control group is shown in Fig. 1. The log-rank test indicated that the ADHD + CD group had significantly lower disease-free survival rates for unipolar depressive disorder and bipolar disorder. Cox regression analysis with adjustment of age, gender, residence location, and level of urbanization revealed that the ADHD + CD group, ADHD + ODD group, and ADHD-alone group had increased risks of unipolar depressive disorder (HR: 44.34, 95%CI: 23.95–71.36; HR: 18.76, 95%CI: 7.87–44.71; HR: 13.01, 95%CI: 8.99–18.82) and bipolar disorder (HR: 14.39, 95%CI: 4.00–51.80; HR: 8.32, 95%CI: 1.06–65.32; HR: 5.24, 95%CI: 2.44–11.24) compared to the control group (Table 2).

3. Discussion

Our results supported the hypothesis that ADHD adolescents had an increased risk of developing both unipolar depression and