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Further Evidence that Pediatric-Onset Bipolar Disorder Comorbid with ADHD Represents a Distinct Subtype: Results from a Large Controlled Family Study

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Abstract

We used familial risk analysis to clarify the diagnostic comorbidity between pediatric BP-I disorder and ADHD, testing the hypothesis that pediatric BP-I disorder comorbid with ADHD represents a distinct subtype. Structured diagnostic interviews were used to obtain DSM-IV psychiatric diagnoses on first-degree relatives (n=726) of referred children and adolescents satisfying diagnostic criteria for BP-I disorder (n=239). For comparison, diagnostic information on the first-degree relatives (N=511) of non-bipolar ADHD children (N=162) and the first degree relatives (N=411) of control children (N=136) with neither ADHD nor BP-I disorder were examined. BP-I disorder and ADHD in probands bred true irrespective of the comorbidity with the other disorder. We also found that the comorbid condition of BP-I disorder plus ADHD also bred true in families, and the two disorders co-segregated among relatives. This large familial risk analysis provides compelling evidence that pediatric BP-I disorder comorbid with ADHD represents a distinct familial subtype.

Keywords

bipolar disorder; attention-deficit hyperactivity disorder; family-genetic; children

Introduction

A bidirectional and robust comorbidity between pediatric bipolar (BP)-I disorder and attention deficit hyperactivity (ADHD) has been well documented in pediatric and adult studies in both clinical and epidemiological samples (Biederman et al 2001; Kessler et al 2006; Singh et al 2006; Lus & Mukaddes 2009; Arnold et al 2011). Arnold et al (2011) examined the comorbidity between ADHD and bipolar spectrum disorders (BPSDs) in the

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Longitudinal Assessment of Manic Symptoms (LAMS) study. Of 707 children, 421 had ADHD alone, 45 had BPSD alone, 117 had both ADHD and BPSD, and 124 had neither. The co-occurrence of the ADHD plus BPSD was associated with poorer global functioning, greater symptom severity, more additional comorbidity and higher rates of psychiatric hospitalizations than for either single disorder.

Similar findings were reported by Lus and Mukaddes (2009) who found that 8.3% of a sample of 121 youth 6–16 years with ADHD also met diagnostic criteria for bipolar disorder and that those affected with this comorbidity had significantly more pathological scores on multiple CBCL scales and on the YMRS than other ADHD youth without this comorbidity. Bernardi et al (2010) identified a rate of co-occurrence of ADHD with bipolar disorder of 18% lifetime and 10% current in a sample of 100 adult bipolar outpatients aged 18–30 years. Patients with ADHD plus comorbid bipolar disorder had a significantly earlier onset of mood disorder, higher number of previous mood episodes, and significantly higher impulsivity than bipolar patients without ADHD. Moreover, the comorbidity between ADHD and bipolar disorder has been confirmed by meta-analysis, indicating that its existence cannot be attributed to the diagnostic traditions or methodological approaches of any single research group (Kowatch et al 2005).

By providing information that is external to the clinical picture, family-genetic studies are uniquely suited for the evaluation of complicated diagnostic pictures such as that which occurs when ADHD and bipolar disorder co-occur comorbidly (Faraone et al 1999). This is especially relevant for disorders like ADHD and BP-I disorder, which have been documented to co-occur in families (Faraone, Biederman, and Wozniak. Examining the Comorbidity between Attention Deficit Hyperactivity Disorder and Bipolar Disorder: A Meta-Analysis of Family-Genetic Studies. *Am J Psychiatry* 2012; Faraone, Biederman, and Wozniak. Examining the Comorbidity between Attention Deficit Hyperactivity Disorder and Bipolar Disorder: A Meta-Analysis of Family-Genetic Studies. *Am J Psychiatry* in press). In a series of small studies of probands with ADHD, we showed that while BP-I disorder was elevated among relatives of ADHD children, this risk was limited to relatives of those children with both disorders. Results also showed that ADHD and bipolar disorder cosegregated among relatives (Faraone et al 1998; Faraone et al 2001). Similar results were obtained in a pilot study of children with BP-I disorder (Wozniak et al 1995). In that study, we showed that first-degree relatives of probands with both BP-I disorder and ADHD had higher rates of both ADHD and BP-I disorder than either the relatives of children with BP-I disorder only or relatives of control children. We also showed that ADHD and BP-I cosegregated among relatives (Wozniak et al 1995). Although this pattern of familial aggregation was most compatible with the hypothesis that BP-I disorder plus ADHD represents a distinct genetic subtype of either ADHD or BP-I disorder (Pauls et al 1986; Faraone et al 1997), this conclusion was limited by the small sample sizes of those studies, as well as the lack of a study sample of children with BP-I disorder without ADHD.

The main aim of this study was to use familial risk analysis to re-evaluate the familial association between pediatric BP-I disorder and ADHD in a well-powered sample that included children with BP-I disorder with and without comorbid ADHD, children with ADHD without comorbid BP-I disorder, and Control children without ADHD or BP-I disorder. Based on our previous work, we hypothesized that when BP-I disorder and ADHD are not comorbid with one another, they would breed true, that is, relatives of probands with BP-I disorder would have higher rates of BP-I disorder than relatives of probands with ADHD, who would have high rates of ADHD. We further hypothesized that BP-I disorder and ADHD would cosegregate among the relatives of probands with BP-I and ADHD. To the best of our knowledge, this study is the most comprehensive and largest evaluation of this issue.

Materials and Methods

Detailed study methods have been previously described (Wozniak et al., 2012 submitted). Briefly, families were recruited and assessed at the Clinical and Research Program in Pediatric Psychopharmacology at the Massachusetts General Hospital based on the presence of a diagnosis of BP-I disorder in proband youth 6–17 years of age of both sexes (Wozniak et al 2005; Wozniak et al 2010). Comparators were youth with ADHD and controls without ADHD or BP-I disorder of similar age and sex along with their first degree relatives (Biederman et al 1992; Biederman et al 1999). All studies used the same assessment methodology regardless of the disorder used to classify probands as cases. We recruited 239 bipolar-I probands (726 first-degree relatives). From 522 families participating in our case-control ADHD family studies we randomly selected 162 non-bipolar, ADHD (511 first-degree relatives) and 136 non-bipolar, non-ADHD control probands (411 first-degree relatives) so that the age and gender distribution were similar to that of the bipolar-I probands. ADHD probands with co-morbid bipolar disorder were not included in the present analyses. All study procedures were reviewed and approved by the subcommittee for human subjects of our institution. After complete description of the study to the subjects, all subjects' parents or guardians signed written informed consent forms and children older than 7 years of age signed age appropriate written assent forms.

Ascertainment Method

Potential BP-I probands were ascertained from our clinical service, referrals from local clinicians or self-referral in response to advertisements in the local media. To avoid biasing our sample toward familial cases of bipolar disorder, all probands were ascertained blind to the diagnostic status of their relatives. Subjects were administered a phone screen reviewing symptoms of DSM-IV BP-I disorder and, if criteria were met, were scheduled for a face-to-face structured diagnostic interview. In addition to the structured diagnostic interview, an expert clinician (J.W.) met with each potential proband and his or her parents for a clinical interview in order to confirm the diagnosis of bipolar-I disorder using the Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS) mania module. We have published data on the convergence of these clinical interviews with our structured interview diagnosis on the first 69 cases. We reported a 97% agreement between the structured interview and clinical diagnosis in an analysis of 69 children (Wozniak et al 2003).

As previously reported (Biederman et al 1992; Biederman et al 1999; Wozniak et al 2010), ADHD cases were identified from either a major academic medical center, where we selected ADHD subjects from referrals to a pediatric psychopharmacology program, or from a Health Maintenance Organization, in which ADHD subjects were selected from pediatric clinic outpatients. Controls were ascertained from outpatients referred for routine physical examinations to pediatric medical clinics at each setting, identified from their computerized records as not having ADHD. Screening procedures were similar to those described for the recruitment of the BP-I probands with the exception that we queried about ADHD (and not BP-I disorder) in the initial telephone screening and each proband was not assessed clinically.

Diagnostic Procedures

Psychiatric assessments of subjects younger than 18 years were made with the KSADS-E (epidemiologic version) (Orvaschel 1994) and assessments of adult family members were made with the Structured Clinical Interview for DSM-IV (SCID) (First et al 1997) supplemented with modules from the KSADS-E to cover childhood disorders. Diagnoses were based on independent interviews with mothers and direct interviews with children

older than 12 years of age. Data were combined such that endorsement of a diagnosis by either report resulted in a positive diagnosis.

Interviews with both the KSADS-E and SCID were conducted by extensively trained and supervised psychometricians with undergraduate degrees in psychology. This training involved several weeks of classroom instruction of interview mechanics, diagnostic criteria and coding algorithms. They also observed interviews by experienced raters and clinicians and were observed while conducting interviews during the final training period. In addition, all diagnoses were reviewed by a sign-off committee of experienced board-certified child and adolescent psychiatrists or clinical psychologists. The interviewers as well as the committee members were blind to the subjects' ascertainment status, ascertainment site, and data collected from other family members. We computed kappa coefficients of agreement by having experienced clinicians diagnose subjects from audio-taped interviews made by the assessment staff. Based on 500 interviews, the median kappa coefficient between raters and clinicians was 0.99. For individual diagnoses the kappas were ADHD (0.88), conduct disorder (1.0), major depression (1.0), bipolar (0.95), separation anxiety (1.0), agoraphobia (1.0), panic (0.95), substance use disorder (1.0), and tics/Tourette's (0.89). The median agreement between individual clinicians and the clinical review committee was 0.87 and for individual diagnoses was ADHD (1.0), conduct disorder (1.0), major depression (1.0), bipolar (0.78), separation anxiety (0.89), agoraphobia (0.80), panic (0.77), substance use disorder (1.0), and tics/Tourette's (0.68).

Children and adolescents were diagnosed with bipolar-I disorder according to DSM-IV criteria. The DSM-IV requires subjects to meet criterion A for a distinct period of extreme and persistently elevated, expansive or irritable mood lasting at least 1 week, plus criterion B, manifested by three (four if the mood is irritable only) of seven symptoms during the period of mood disturbance. To ensure that the B criterion symptoms were concurrent with A criterion mood disturbance, subjects were directed to focus on the worst or most impairing episode of mood disturbance while being assessed for the presence of the confirmatory B criterion symptoms. That is, the subject was asked to consider the time during which the screen was at its worst for the purpose of determining whether the remaining symptoms were also evident at the same time as the screening item. Also recorded was the onset of first episode, the number of episodes, offset of last episode, and total duration of illness. Any subject meeting criteria for BP-II or BP-NOS was not included in this study. To gauge a distinct episode, our interviewers asked for 'a distinct period (of at least 1 week) of extreme and persistently elevated, expansive or irritable mood' and further required that the irritability endorsed in this module is 'super' and 'extreme.'

Statistical Analysis

Differences in demographics and clinical characteristics were assessed using ANOVA for continuous outcomes, Pearson's χ^2 for binary outcomes, and Kruskal Wallis for SES. The Kaplan-Meier cumulative failure function was used to calculate survival curves and cumulative, lifetime risk in relatives. Cox proportional hazard models were used to calculate the risk of BP-I disorder and ADHD in relatives. Because no relative of the BP-I only probands had both BP-I and ADHD, we used a random number generator to choose one family member from this group to have both BP-I and ADHD. The family member who had the lowest random number was chosen and the sample's average age of onset was used. Across all models, we used robust estimates of variance to account for the non-independence of the sample resulting from the correlation between family members. Data are expressed as mean $\pm$ standard deviation (SD) unless otherwise specified. All tests were two-tailed, and our alpha level was set at 0.05 for all analyses, unless otherwise noted. We calculated all statistics using STATA, version 12.0.

Results

BP-I probands were stratified by the presence (BP-I+ADHD) or absence (BP-I) of comorbid ADHD (BP-I+ADHD). Analyses were made among the following groups: 19 BP-I (N=61 first degree relatives), 220 probands with BP-I + ADHD (N=626 first-degree relatives); 162 probands with ADHD (without bipolar disorder) (N=511 first-degree relatives); 136 control probands with neither bipolar disorder nor ADHD (N=411 first-degree relatives).

Demographic and clinical characteristics of the sample are presented in Table 1. There were no differences in sex distribution between the proband groups. However, we found small but significant differences in age, with the BP-I probands being somewhat older than other probands. There were also small but statistically significant differences in the ethnic and socio-economic backgrounds of the families. The ADHD families (BP-I+ADHD, and ADHD) had a lower SES and the BP-I+ADHD had more ethnic diversity. Accordingly, all subsequent tests were adjusted for SES, race, and proband age.

As shown in Figure 1, the prevalence of BP-I disorder among relatives of BP-I and BP-I + ADHD probands were similar to one another and significantly higher than the prevalence of BP-I disorder among relatives of both the ADHD and the healthy control probands. The prevalence of BP-I disorder was nearly identical in the latter two groups. The prevalence of ADHD among relatives of ADHD and BP-I + ADHD probands were also similar to one another and significantly higher than the prevalence of ADHD among relatives of both the BP-I and Control probands (Figure 2). The latter two groups did not differ from one another.

Among relatives of the BP-I + ADHD probands, 46% (n=33) of the 71 relatives with BP-I, also had ADHD and 20% (n=111) of the 555 relatives without BP-I, had ADHD. As shown in Figure 3, the prevalence of BP-I + ADHD among relatives of BP-I + ADHD probands was significantly higher than the prevalence of BP-I + ADHD among relatives of BP-I only, the ADHD and the healthy control probands. These results show that ADHD and BP-I cosegregate among the relatives of BP-I + ADHD probands.

Discussion

We can draw several conclusions from this large familial risk analysis of children with BP-I, ADHD, both disorders and neither: 1) when these disorders are not comorbid with one another, pediatric BP-I disorder and ADHD breed true in families; 2) pediatric BP-I disorder comorbid with ADHD also breeds true in families; and 3) pediatric BP-I disorder and ADHD are more likely to occur together in relatives of BP-I + ADHD probands. These results are consistent with our hypothesis that pediatric BP-I disorder represents a distinct developmental subtype that is familially separate from the non-comorbid forms of BP-I disorder and ADHD.

Our finding showing that the familiarity of ADHD was not affected by the comorbidity with BP-I disorder is consistent with the hypothesis that the symptoms of ADHD in these subjects reflected the presence of true ADHD and not that these symptoms were secondary to BP-I disorder. This is so considering that a large body of literature documents the high familiarity of ADHD in pediatric and adult samples (Faraone & Mick 2010; Franke et al 2011). Likewise, the familiarity of BP-I disorder in the proband was not affected by the comorbidity with ADHD is consistent with the hypothesis that the symptoms of BP-I disorder in these subjects reflected the presence of true BP-I disorder and not that these symptoms were secondary to ADHD. This is so considering that a large literature documents that BP-I disorder is highly familial in pediatric (Strober et al 1988; Geller et al 2006) and adult samples (Tsuang & Faraone 1990; Tsuang et al 2004). Taken together, these findings

suggest that our probands satisfying diagnostic criteria for ADHD and BP-I disorder were in fact affected by these disorders.

Our findings are consistent with prior work that suggested a genetic link between BP-I disorder and ADHD. For example, Geller et al. (2006) reported that the risk for BP-I disorder in relatives of BP-I disorder probands with comorbid ADHD was higher than in those without ADHD. Likewise, Rende et al. (2007) reported that 33% of children with BP-I disorder had a family history of ADHD. Faraone et al. (1997) showed that, in a pooled analysis of five studies, offspring of bipolar parents had a significantly greater risk for ADHD (15%) compared with children of controls (5%). Similarly, a pooled analysis of six family studies of ADHD reported an increased risk for BP-I disorder among relatives of ADHD probands (2.6%) compared with control probands (1.3%) (Faraone et al 1997). Molecular genetic evidence also points to a relationship between BP-I disorder and ADHD in the form of the dopamine transporter gene, which has been associated with both bipolar disorder (Greenwood et al 2006; Mick et al 2008) and ADHD (Brookes et al 2006; Asherson et al 2007).

Prior studies, however, were limited because they were based on family studies of ADHD having no cases of BP-I disorder without ADHD or family studies of BP-I disorder having no cases of ADHD without BP-I disorder. This made it difficult to determine if diagnoses of one disorder could be attributed to diagnostic confusion with the other disorders. If the familial co-transmission of ADHD and BP-I disorder were due to diagnostic confusion, we would expect each disorder to be elevated among probands regardless of comorbidity. The present results show that this is not the case. When ADHD occurs in children without BP-I disorder, their relatives are only at risk for ADHD and when BP-I disorder occurs in children without ADHD, their relatives are only at risk for BP-I disorder. This provides strong evidence against the diagnostic confusion hypothesis and also suggests that when these disorders occur separately, they do not share genetic causes.

Consistent with our pilot studies (Wozniak et al 1995; Faraone et al 2001), we also found that BP-I + ADHD breeds true and is familially distinct from ADHD and BP-I when the two disorders are not comorbid. These findings of cosegregation between BP-I disorder and ADHD in relatives indicate that cosegregation can be documented independently of ascertainment source, whether probands were selected for a study of ADHD or a study of BP-I disorder.

The cosegregation findings suggest that BP-I + ADHD is a distinct familial entity and, perhaps, a distinct disorder. Consistent with this idea, studies in both adults and youth have linked the comorbid condition of BP-I disorder plus ADHD to early age of onset of BP-I disorder (Bernardi et al 2010). Faraone et al. (1997) found higher rates of ADHD in subjects with childhood onset BP-I disorder compared with subjects with adolescent onset BP-I disorder. Those findings were consistent with West et al.'s (1996) report that 57% of adolescents with BP-I disorder also had ADHD whereas the prevalence reported in pre-adolescent BP-I disorder samples across sites is much higher, ranging from 70–98% (Wozniak et al 1995; Findling et al 2001; Rende et al 2007). These results suggest that co-occurrence with ADHD may be a marker of early onset (not just pediatric age of onset, but pre-pubertal age of onset).

Studies of adults with BP-I disorder also suggested that ADHD may be a marker for an early onset subtype. Winokur et al. (1993) reported that, among adults with BP-I disorder, a history of comorbid ADHD was only evident in those subjects with onset of bipolar disorder before 19 years of age. The mean age of onset of BP-I disorder in those with a history of childhood ADHD was 12.1 years (Winokur et al 1993). Nierenberg et al. (Nierenberg et al

2005) reported that the prevalence of ADHD in a large sample of adults with bipolar disorder (N=1000) was 9.5% and that these adults had distinct features of BP-I disorder including early onset, shorter periods of wellness (chronicity), greater comorbidity and overall a worse course. Chang et al.'s study of children of adults with BP-I disorder, found that BP-I disorder in children was associated with early onset BP-I disorder in the parent *and* a parental history of ADHD (Chang et al 2003). In that study, the age of onset of mania in adults with BP-I disorder and a history of ADHD was 11.3 years of age.

The idea that ADHD comorbid with BP-I disorder is a distinct disorder is further supported by emerging neurobiological findings. Genetic evidence points to a relationship between BP-I disorder and ADHD in studies suggesting that the dopamine transporter gene is associated with both BP-I disorder (Greenwood et al 2006; Mick et al 2008) and ADHD (Brookes et al 2006; Asherson et al 2007). In a magnetic resonance spectroscopy study, Moore et al. (2006) found that the Glx-to-Ino ratio distinguished children with BP-I disorder plus ADHD from those with ADHD alone. These data support the hypothesis that children with the comorbid state of BP-I disorder plus ADHD have distinct brain and genetic underpinnings compared with those with ADHD without this comorbidity.

Our findings should be considered in the context of methodological limitations. Although we did not administer structured diagnostic interviews directly to children younger than 12 years of age, a clinical diagnosis of BP-I disorder in probands was corroborated by clinical assessment by an expert clinician prior to study inclusion (Wozniak et al 2003). Also, we did not concurrently enroll comparison families but relied instead upon existing samples of ADHD and non-ADHD families. However, because all subjects were recruited from the same catchment area using the same ascertainment schema and research assessments, it is unlikely that the sample definition accounts for the findings presented here. The fact that the BP-I only group was significantly smaller than the other groups is also a limitation as uneven sample sizes may have reduced the statistical power of the analyses. Finally, because this sample was clinically referred and primarily Caucasian, these results may not generalize to non-referred children or to families of other ethnicities.

With these considerations in mind, we report that both ADHD and BP-I disorder breed true in relatives irrespective of the comorbidity with the other disorder. We also report that the comorbid state of BP-I disorder plus ADHD also breeds true. Because BP-I disorder plus ADHD was found predominantly among the relatives of probands with BP-I disorder plus ADHD, and virtually all of the BP-I disorder in the relatives of probands with BP-I disorder plus ADHD occurred comorbidly with ADHD, a pattern of cosegregation is suggested. These findings support the hypothesis that BP-I disorder plus comorbid ADHD is a distinct familial subtype of either BP-I disorder or ADHD. Further studies addressing genetic association and neuroimaging of this group may yield important information regarding course, treatment, and the neurobiology of BP-I disorder plus ADHD to determine if this combined condition should be considered to be a distinct disorder.

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Figure 1.
Morbid Risk of BP-I in 1st Degree Relatives

Figure 2.
Morbidity Risk of ADHD in 1st Degree Relatives

Figure 3.
Morbidity Risk of BP-I + ADHD in 1st Degree Relatives

Table 1

Clinical and Demographic Characteristics (N=2182)

Probands	BP-1 Families n=19		BP-1 + ADHD Families N=220		ADHD Families n=162		Control Families n=136		Test Statistic	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age (years)	12.7	3.5	10.5	3.2	10.6	3.0	10.7	3.0	F	df
Past GAF	40.5	6.6	40.8	5.8	50.7	7.3	70.5	8.5	3.03	3, 533
Current GAF	50.8	7.4	46.3	5.6	57.4	8.2	73.3	7.3	518.1	2, 531
	N	%	N	%	N	%	N	%	426.3	2, 531
Gender (% male)	12	63	162	74	121	75	99	73	1.2	2
Parents	n=36		N=409		n=323		n=269		χ^2	df
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df
Age (years)	44.9	4.7	42.5	6.5	41.3	6.4	41.6 ±	5.8	5.4	2, 1035
Past GAF	53.2	10.0	51.6	9.8	56.9	12.6	63.5	12.4	59.5	2, 1031
Current GAF	65.3	7.7	63.2	7.9	68.5	9.5	72.9	7.9	74.8	2, 983
	N	%	N	%	N	%	N	%	χ^2	df
Gender (% male)	16	44	196	48	161	50	133	49	0.4	2
Siblings	n=25		N=217		n=188		n=142			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df
Age (years)	13.0	4.9	12.2	4.5	13.7	5.9	12.9	5.1	3.03	2, 568
Past GAF	61.8	10.6	57.1	9.4	61.8	12.0	65.9	10.7	20.11	2, 568
Current GAF	66.1	7.3	62.6	7.6	67.9	10.8	71.1	8.4	28.2	2, 567
	N	%	N	%	N	%	N	%	p<0.001	
Gender (% male)	9	36	103	47	103	55	74	52	3.2	2
Total	n=116		N=846		n=673		n=547			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	χ^2	df
SES	1.5	0.7	1.8	0.9	1.8	1.0	1.5	0.8	12.3	3
Race/Ethnicity	N	%	N	%	N	%	N	%	χ^2	df
Caucasian	80	100	797	94	667	99	536	98	49.9	6
									<0.001	

Probands	BP-1 Families n=19		BP-1 + ADHD Families N=220		ADHD Families n=162		Control Families n=136		Test Statistic		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
African-American	0	0	32	4	6	1	7	1			
More than 1	0	0	15	2	0	0	0	0			
Unknown	0	0	2	<1	0	0	4	1			