



Bipolar disorder co-morbidity in children with attention deficit hyperactivity disorder

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ABSTRACT

The present study aimed at: (1) exploring rate and clinical features of superimposed bipolar disorder (BD) in Italian children with attention deficit hyperactivity disorder (ADHD), compared with a community sample, matched for age and gender; (2) exploring predictors of BD in ADHD children, by comparing ADHD children with or without superimposed BD. We studied 173 consecutive drug-naïve outpatients with ADHD (156 males and 17 females, mean age of 9.2 ± 2.3 years, age range 6–17.5 years), diagnosed with a clinical interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL)); the control group consisted of a community-based sample of 100 healthy children. The rate of children with a diagnosis of BD was higher in the ADHD group (29/173, 16.7%) compared with controls (1/100, 1%), ($P < 0.001$). Among the 29 children with ADHD + BD, 16 (55.2%) had a Bipolar Disorder–Not Otherwise Specified (BD–NOS), and 11 (37.9%) showed ultrarapid cycling. Compared with children with ADHD without BD, they showed a higher rate of combined sub-type (21/29, 72.4%), a higher score at ADHD–Rating Scale (total score and hyperactivity subscale), higher rates of major depression, oppositional defiant disorder and conduct disorder. In summary, children with ADHD present a higher risk for developing a superimposed BD. The identification of clinical features with an increased risk of BD can improve diagnosis, prognosis and treatments.

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1. Introduction

A major feature of juvenile bipolar disorder (BD) is its frequent ‘atypicality’, compared with adult ‘standards’, in terms of presentation, course and pattern of co-morbidity (Wozniak et al., 1995; Findling et al., 2001; Masi et al., 2006a). Classical, adult-like symptomatology of manic-depressive illness, with clear episodes of euphoric mood and inflated self-esteem, alternated with depressive episodes is not frequent in children with BD (Geller and Luby, 1997). Another marker of the earliest forms of BD is the high co-morbidity with disruptive behaviour disorders, namely Attention Deficit Hyperactivity Disorder (ADHD) (Faraone et al., 1997; Kim and Miklowitz, 2002; Galanter and Leibenluft, 2008). The rate of this co-morbidity is still debated in the literature, ranging from 30% to 90% (Kim and Miklowitz, 2002). Furthermore, even in adult patients, ADHD and BD co-morbidity is well established (47% of ADHD and 21% of bipolar adult patients, according to a meta-analysis), even though still understudied (Wingo and Gaemi, 2007). Differential diagnosis

among early-onset mania, severe ADHD, and the co-occurrence of both the disorders may be very difficult, given the overlap of some symptoms (hyperactivity, impulsivity/aggressiveness, distractibility and emotional lability) (Kim and Miklowitz, 2002; Galanter and Leibenluft, 2008).

The relationship between ADHD and BD is far from clear. Three models have been suggested to explain the overlap between paediatric BD and ADHD: (a) ADHD symptoms be a prodrome to paediatric BD in some cases, (b) BD and ADHD are distinct disorders but share an association with emotional difficulty in childhood, and (c) BD may be a severe variant of personality traits in which an underlying dysfunction in affective and cognitive circuitry associated with emotion regulation causes both temperamental difficulties and clinical symptoms (West et al., 2008). Recent evidence supports the notion that ADHD–BD co-morbidity has a strong and specific biological basis (Biederman et al., 2008; Pavuluri et al., 2009; Lopez-Larson et al., 2009).

The issue is not merely nosological, because ADHD co-morbidity affects several clinical features of BD, and it can be a meaningful predictor of prognosis and treatment (Biederman et al., 1996; Faraone et al., 1997; Masi et al., 2004a,b). In our previous studies, we explored the effect of ADHD co-occurrence on BD phenomenology and

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treatment by analysing a sample of children and adolescents with BD, and stratifying them according to the ADHD co-morbidity. According to these findings, ADHD is associated with an earlier onset of BD (Masi et al., 2007), a chronic course and an irritable mood (Masi et al., 2006b, c), a greater resistance to treatments (Masi et al., 2004a), a more frequent diagnosis of Bipolar Disorder-Not Otherwise Specified (BD-NOS) (Masi et al., 2007) and a lesser efficacy of lithium (Masi et al., 2010). Most of these features are consistent with the definition of severe mood dysregulation, according to Leibenluft and co-workers (Leibenluft et al., 2003).

These previous studies did not explore the occurrence of BD in a sample of children with ADHD. According to a review article by Spencer et al. (2001), children with ADHD are 10 times as likely to develop BD than age-matched and gender-matched controls. However, ethnic and sociocultural differences are meaningful in the emergence of early onset BD (Kennedy et al., 2004).

The present study was aimed at: (1) assessing the rate and the clinical features of BD in a large, consecutive sample of Italian children with co-morbid ADHD, compared with a control, epidemiological sample of children attending elementary and junior high schools, matched for age and gender; (2) exploring possible elements associated with an increased risk of BD, comparing ADHD children with or without superimposed BD. Our hypotheses were that BD is more frequent in a sample of ADHD, consistently with data from the literature; that BD occurrence is associated with a greater severity of ADHD; and that the ADHD–BD co-occurrence is associated with a heavier co-morbidity.

2. Methods

2.1. Participants

We studied 173 consecutive drug-naïve Caucasian outpatients with ADHD (156 males and 17 females, mean age of 9.2 ± 2.3 years, age range 6–17.5 years), diagnosed at the Clinic for Developmental Neurology and Psychiatry 'La Scarpetta' in Rome, from January 2004 to December 2008. None of these patients was included in previous studies on BD from our group. The percentage of females (10.8%) was lower compared with the percentage found in the North-American population of children with ADHD, but similar to those found in European studies (Buitelaar et al., 2006).

The control group included 100 healthy Caucasian children matched for age and sex, (85 males and 15 females, mean age 9.1 ± 1.8 years, age range 6–17 years), recruited from a community-based survey, attending seven elementary and junior high schools from the same urban area of Rome.

Both children and parents in the clinical sample of ADHD patients separately received a semi-structured psychiatric interview, the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), by an experienced child psychiatrist (RD). The K-SADS-PL is a structured interview organised in such a way as to explore the presence or absence of each of the symptoms in different psychiatric syndromes, according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV). All the children in the ADHD group also received an additional routine diagnostic assessment, including the ADHD-Rating Scale (ADHD-RS) (DuPaul et al., 1998) adapted for the Italian population (Marzocchi and Cornoldi, 2000), filled out by parents and school teachers; the Wechsler Intelligence Scale for Children–Revised (WISC-R) (Wechsler, 1973) (all children with Intelligence Quotient (IQ) < 70 were excluded); and a standardised battery for the diagnosis of dyslexia for Italian children (Job et al., 1995). Medical history, neurological and physical examinations and electroencephalogram during sleep were also used to exclude co-morbid medical and neurological conditions. The assessment of familial psychiatric disorders was based on careful anamnestic historical information with both the parents.

All the patients with ADHD, who received a diagnosis of BD according to K-SADS-PL, were also assessed with the Young Mania Rating Scale (YMRS) (Young et al., 1978) to further explore manic symptomatology. The YMRS has 11 items and is based on the patient's subjective report of clinical condition over the previous 2 days, and on clinical observation during the course of the clinical interview. Items are graded on a 0–8 scale (irritability, speech, thought content, and disruptive/aggressive behaviour) or 0–4 scale (the remaining items). The diagnosis of BD was confirmed when the DSM-IV criteria for bipolar I or II disorder or accepted criteria for BD-NOS were fulfilled and the YMRS score was above 14. In our study, we defined BD-NOS according to DSM-IV, including in this sub-type patients with a clear start point of very rapid alternation between manic and depressive symptoms that do not meet the duration criteria for manic or depressive symptoms, or presenting an abnormal mood (sadness, anger or elated mood) and hyperarousal associated with a minimum of three manic symptoms (one less than the DSM-IV B criteria) (Masi et al., 2006a, 2007). Daily cycling was also considered, defining

the manic or depressive episode when at least four symptoms lasted at least 4 h per day (Geller et al., 2007).

The epidemiological control group was assessed for BD using the specific items of K-SADS-PL, but other co-morbidities were not investigated.

Written informed consent for this study was obtained from the parents of all the patients.

2.2. Data analyses

Children with ADHD and control subjects were compared using chi-square analysis on categorical variables and an analysis of variance (ANOVA) and paired *t*-tests on continuous variables with Fisher's protected least significant difference (PLSD) *post-hoc* comparisons on continuous variables. Owing to the multiple comparisons and the number of patients, our results are prone both to type I and type II errors. Statistical analyses were based on commercial software (Statview-5,[®] SAS Corporation, Cary, NC; Stata-8,[®] Stata Corporation, College Station, TX, USA).

3. Results

The rate of children with a diagnosis of BD was significantly higher in the ADHD group (29/173, 16.7%) compared with controls (1/100, 1%), ($\chi^2 = 16.1$, $P < 0.001$).

Patients with ADHD plus BD, ADHD without BD and controls did not differ according to gender distribution, age and SES (see Table 1).

Among the 29 children with ADHD plus BD, 16 (55.2%) had a BD-NOS (all males, mean age 9.2 ± 2.3 years), 10 (34.5%) had BD-II (nine males and one female, mean age 9.5 ± 2.6 years), while only three (10.3%) presented BD-I (two males and one female, mean age 8.9 ± 0.2 years). Eleven subjects (37.9%) showed rapid cycling (nine males and two females, mean age 9.3 ± 2.1 years, three with BD-I and eight with BD-II), seven of them had ultradian cycling (six males and one female, mean age 10.5 ± 2.5 years, two with BD-I and five with BD-II). One 7-year-old male from the control group (1%) showed a BD-NOS.

In the subjects with ADHD and BD, 21/29 (72.4%) presented the combined sub-type, 7/29 (24.1%) the hyperactive–impulsive sub-type and 1/29 (3.5%) the inattentive sub-type. The percentage of combined sub-type of ADHD was significantly higher in children with co-morbid BD compared with children without BD ($\chi^2 = 6.39$, $P < 0.05$).

When children with ADHD with or without BD were compared, no difference between groups were found according to IQ, as well as according to the single subtests of the WISC-R. The ADHD children with co-morbid BD, compared with children with ADHD without co-morbid BD, showed higher scores at both ADHD-RS total score and at the hyperactivity–impulsivity subscale (see Table 2). Regarding co-morbidities, rates of anxiety disorders, dystimic disorder and learning disabilities did not differ between children with ADHD and BD and children with only ADHD. On the contrary, children with ADHD plus BD had a higher rate of major depression, oppositional defiant disorder (ODD) and conduct disorder (CD), compared with those without BD (Table 2).

In the 29 ADHD children with superimposed BD, 11 presented very early (first 2 years of life) and severe hyperactivity, with major irritability in two cases and aggressiveness in two cases. Euphoria since 2–3 years of age was reported in three children. Depressive

Table 1

Patients with attention deficit hyperactivity disorder (ADHD) without bipolar disorder (BD), with ADHD plus BD, and controls: Demographic data.

	ADHD without BD	ADHD + BD	Controls	χ^2/F	df	p<
	N = 144	N = 29	n = 100			
Boys	N = 130 (90.3%)	N = 26 (89.7%)	N = 85 (85.0%)	1.7	2	NS
Age, mean \pm SD	9.2 \pm 2.3	9.4 \pm 2.2	9.1 \pm 1.8	0.2	272	NS
Socioeconomic status	66.9 \pm 20.8	72.3 \pm 20.4	63.3 \pm 20.5	2.3	272	NS

* = statistically significant ($p < .05$); NS = not significant.

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