Published in final edited form as:

J Affect Disord. 2013 February 15; 145(1): 70–76. doi:10.1016/j.jad.2012.07.014.

Attention deficit hyperactivity disorder characteristics: II. Clinical correlates of irritable mood

Paul J. Ambrosini, M.D.^{a,*}, David S. Bennett, Ph.D.^a, and Josephine Elia, M.D.^b

^aDivision of Child & Adolescent Psychiatry, Drexel University College of Medicine, Philadelphia, PA

^bDepartment of Child & Adolescent Psychiatry, The Children's Hospital of Philadelphia and Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania and Children's Hospital of Philadelphia, Philadelphia, PA

Abstract

Background—This study describes the relationship of irritable mood (IRR) with affective disorders in youths with attention deficit hyperactivity disorder (ADHD).

Methods—Five hundred ADHD subjects were assessed with the childhood version of the Schedule for Affective Disorder & Schizophrenia. Subjects were in a genetic ADHD protocol and limited to those of Caucasian/European descent.

Results—The most prevalent concurrent diagnoses were oppositional defiant disorder (ODD) (43.6%), minor depression/dysthymic disorder (MDD) (18.8%), and generalized anxiety (13.2%)/overanxious disorder (12.4%). IRR subjects (21.0%) compared to the non-IRR (NIRR) group had higher rates of all affective disorders (76.2% vs. 9.6%) and ODD (83.8% vs. 32.9%) but lower rates of hyperactive ADHD (1.9% vs. 8.9%). Among those without comorbidities, 98.3% were NIRR. Logistic regression found IRR mood significantly associated with major depressive disorder (odds ratio [OR]: 33.4), MDD (OR: 11.2), ODD (OR: 11.6), and combined ADHD (OR: 1.7) but not with anxiety disorders. Among symptoms, it associated IRR mood with a pattern of dysthymic and ODD symptoms but with fewer separation anxiety symptoms. Diagnostic and symptomatic parameters were unaffected by demographic variables.

Limitations—Potential confounders influencing these results include patient recruitment from only one clinical service; a cohort specific sample effect because some presumed affective disorders and non-Caucasians were excluded; and the young mean age (10.2 years) limiting comorbid patterns.

© 2012 Elsevier B.V. All rights reserved.

*Corresponding author: Paul J. Ambrosini, MD Drexel University College of Medicine Division of Child & Adolescent Psychiatry PO Box 45358, Philadelphia, PA 19124 Tel: 215-831-6962 Fax: 215-831-7830 (fax) paul.ambrosini@drexelmed.edu..

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Conflicts of interest: None of the authors has any conflicts to disclose.

Contributors

Dr. Ambrosini was responsible for data management, data analysis, and writing the manuscript.

Dr. Bennett was responsible for data analysis and writing the manuscript.

Dr. Elia conducted the clinical interviews and edited the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi: •.

Conclusions—The prominence of an MDDD pattern suggests this IRR group is appropriate in the DSM V's proposed chronic depressive disorder, possibly with or without temper dysregulation. A new diagnosis of disruptive mood dysregulation disorder may be unwarranted.

Keywords

irritability; ADHD; dysthymia; minor depression; bipolar

1. Introduction

Irritable mood (IRR) has taken center stage in the diagnosis of childhood-onset bipolar disorder. Numerous reports suggest that, in contrast to the “classical” distinct and time-limited periods of irritability and dysphoria, chronic, nonepisodic irritability is characteristic of pediatric bipolar disorder (Kowatch et al., 2005). This conceptualization of pediatric bipolarity emerged from Biederman's work, which first identified the association of nonepisodic irritability with bipolar symptoms in children with attention deficit hyperactivity disorder (ADHD) (Wozniak et al., 1995). As this theme entered the clinical practice of child psychiatry, reports of pediatric bipolarity greatly increased (Blader and Carlson, 2007; Moreno et al., 2007), although some questioned this interpretation of the clinical data (Biederman et al., 1998a; Brotman et al., 2006; Carlson, 1998; McClellan, 2005). This diagnostic issue was further complicated by the fact that irritability is associated not only with bipolar disorder but also with oppositional defiant disorder (ODD), major depressive disorder (MDD), and dysthymic disorder (DD) in youths (Mick et al., 2005). The diagnostic meaning of “rage attacks” or anger episodes in youths also remains unsettled (Carlson, 2007). Both clinical and physiological data regarding IRR are sparse (Leibenluft et al., 2003a).

Leibenluft has suggested interpreting this IRR phenotype as a manifestation of severe mood dysregulation (SMD) (Brotman et al., 2006; Leibenluft et al., 2003b, 2006; Stringaris et al., 2009). Although ongoing research is attempting to clarify the diagnostic parameters of early-onset bipolarity and severe mood disturbances, it is unclear how the symptom of irritability segregates within ADHD samples, how it influences the clinical presentation of ADHD, and whether there is a continuum between more severe rage and less intense IRR. The Diagnostic and Statistical Manual of Mental Disorders V (DSM V) working committee is addressing this issue and has proposed a diagnostic category within the mood disorder section labeled disruptive mood dysregulation disorder (DMDD), based predominately on Leibenluft's work with SMD. This new classification attempts to more clearly differentiate the phenotype of SMD for both treatment and research purposes. The aim of this study was to identify the demographic and clinical characteristics of IRR in youths with ADHD and its relationship with comorbid disorders. Classification issues related to the IRR child are discussed.

2. Method

2.1. Procedures

This study used a cross-sectional design incorporating 500 parent-child triads with one or more ADHD probands. Subjects were recruited from local pediatric and behavioral health clinics for an ADHD genetic study. Patient recruitment was completed over a 55-month period and this sample represented consecutive admissions to the study. All subjects were Caucasian of European descent. Other ethnicities were excluded to maximize the power to detect genetic associations because haplotype frequencies can vary substantially across major world populations (Chang et al., 1996). Approximately 10% of the sample (52/500) were sibling pairs or triads. The initial inclusion/exclusion criteria were verified by phone

screenings: age range, 6 to 18 years; presence of ADHD symptoms; European descent; and availability and willingness of both biological parents to participate in a genetic study. Exclusionary criteria were premature birth (at < 36 weeks) and major medical, neurological, or neuropsychiatric problems including pervasive developmental disorder, mental retardation, psychoses, bipolar disorder, and MDD with symptoms starting prior to ADHD or with ADHD symptoms that occurred primarily during depressed episodes. Children with documented IQ scores < 75 were excluded as were children unable to comprehend or complete the Schedule of Affective Disorders & Schizophrenia-Present State Version (KSADS-P IVR).

A child psychiatrist trained to reliability with the K-SADS-P IVR completed the diagnostic assessments. This K-SADS is keyed to DSM IVR criteria, but where there is overlap with research diagnostic criteria (RDC), RDC take precedence (Spitzer et al., 1978). The K-SADS-P IVR records irritability as a symptom independent of depressed mood. Irritability/anger (subjective) was added as a third primary symptom of major depression to verify whether it was synonymous with depressed mood. KSADS defined irritability/anger as a subjective feeling of bad temper, short temper, crankiness, or annoyance within the context of a mood disorder. This change permitted diagnosing an “irritable affective disorder,” which is a depressive disorder in which irritability replaces depressed mood or pervasive anhedonia as the cardinal symptom. This approach implies that those with IRR affective disorders met standard diagnostic criteria but had IRR mood only, not depressed mood or pervasive anhedonia. The symptoms (being easily angered and easily annoyed) are within the domain of ODD. These are overt symptoms related to being easily bothered by or resentful of others. This is ODD-type irritability as described by Biederman's group (Mick et al., 2005). All ADHD and concurrent comorbid diagnoses analyzed were active at the time of the evaluation; furthermore, subjects were not in treatment by the research team when assessed.

For this study, several diagnostic groupings were calculated: MDDD (minor depression [MD] or dysthymic disorder [DD]); any anxiety disorder (AnyAD); and any depressive disorder (AnyDD). Minor depression is an RDC category that includes the criteria of major depression plus 8 additional symptoms (Table 1). The four ADHD subtypes are labeled inattentive ADHD (ADDI), hyperactive ADHD (ADDH), combined ADHD (ADDC), and ADHD not otherwise specified (ADDN). A detailed list of the diagnoses available with the K-SADS-P IVR is available (Elia et al., 2008). This protocol was approved by the institutional review boards of the participating institutions.

2.2. Statistical Analysis

All K-SADS score sheets were scanned into an SPSS (version 18) database for analyses. Descriptive statistics, including examination of sex differences in demographic variables and comorbidity rates, are presented using *t* tests and chi-square tests. Chi-square analyses were used to examine comorbidity differences between the IRR and NIRR groups of children. A logistic regression controlling for age and gender further examined group differences in comorbid diagnoses and symptoms. Odds ratios and 95% confidence intervals are reported.

3. Results

Demographic parameters and prevalence of IRR are shown in Table 2. The 500 subjects had a mean age of 10.2 (SD 3.2) years and were predominantly male (367/500; 73.4%). The girls were significantly older than the boys (10.8 vs. 10.0, $F=7.4$, $df=1$, $p=0.007$). Using an age cutoff of <13 years for pubertal status, slightly more boys were prepubertal (81.2% vs. 71.4%) and more girls, adolescent (28.6% vs. 18.8%). This finding was compatible with the older age of the girls.

A total of 21.0% (105/500) of the sample had either subjective or overt IRR with nearly identical rates between the sexes (20.7% vs. 21.8%, M: F). Only 13 children had overt irritability, but only 3 had overt IRR without concurrent subjective irritability. Overt IRR is that defined within the bipolar section of the K-SADS. The mean IRR score based on the K-SADS was 3.1 vs. 1.9 (range 1 to 7) in those with and without IRR. The IRR sample was older than the NIRR group (10.8 vs. 10.0, $F=4.26$, $df=1$, $p=0.039$); again, the IRR girls were older than the IRR boys (12.0 vs. 10.3, $F=6.38$, $df=1$, $p=0.01$). The proportional rate of IRR did not significantly differ by sex or pubertal status. Adolescent girls had the highest rate (28.9%) and prepubertal boys, the lowest rate, of IRR (19.8%).

The overall comorbid pattern in this sample was similar to that in a previous analysis of the first 342 subjects recruited into this protocol (Elia et al., 2008). The three most prevalent disorders were ODD (43.6%), minor depression/dysthymia (22.6%), and generalized anxiety disorder (13.2%)/overanxious disorder (12.4%). Overall, 23.6% had AnyDD and 29.0% had AnyAD.

The rates of all affective disorders were similar between the sexes. Simple phobic disorder (11.3% vs. 5.7%) and separation anxiety (12.0% vs. 4.1%) were significantly more common in girls. Girls had a significantly higher overall rate of AnyAD compared with boys (37.6% vs. 25.9%, respectively; $\chi^2=5.9$, $df=1$, $p=0.02$). Among disruptive behavior disorders, more girls met criteria for ADDI ($\chi^2=3.6$, $p=0.057$), but all other ADHD subtypes and ODD were equally prevalent across the sexes.

The symptom of irritability influenced the ADHD comorbid pattern. Those with IRR had a significantly higher number of co-occurring diagnoses inclusive of ADHD than those without IRR (3.1 vs. 1.8, respectively; $F=154.83$, $df=1$, $p<0.001$). Only 2.9% (3/105) of subjects with IRR vs. 44.8% (177/395) of NIRR subjects had ADHD without concurrent comorbid diagnoses. A total of 98.3% (177/180) of ADHD subjects without comorbid disorders were not IRR.

Irritability substantially changed the affective disorder comorbid array. IRR subjects had significantly higher rates of all depressive disorders compared with their NIRR peers. A total of 54.3% of the IRR children but only 9.4% of the NIRR children had a currently active MD or DD; 0.3% (1/395) of the NIRR but 21.0% (22/105) of the IRR subjects had a major depressive disorder (MDD). Overall, 76.2% of IRR and 9.6% of NIRR subjects had any depressive disorder (AnyDD) (Fig. 1). The affective disorder frequency within both IRR subsets remained similar between the sexes. This finding could reflect the young mean age of the sample as the female predominance of affective illness first emerges in the early teen years (Angold et al., 1998).

IRR affected the rates of anxiety disorders more subtly as the rate of having any anxiety disorder now was similar between the IRR/NIRR subsets (34.3% vs. 27.5%, respectively). The rate of anxiety disorders in those with IRR ranged from 1.0% to 16.2%. (A complete list of anxiety and behavioral comorbidities is available in Supplementary Tables 1 and 2.) Whereas the rates of separation anxiety (SA) and AnyAD were higher in girls than in boys, IRR shifted this pattern. NIRR girls had a significantly higher rate of SA (14.4% vs. 4.1%) while IRR girls had a significantly higher rate of AnyAD (51.7% vs. 27.6%) compared to their sex-matched peers (Table 3). IRR had no effect on anxiety disorders in boys.

Irritability greatly increased the overall rate of ODD. A total of 83.8% of the IRR but only 32.9% of the NIRR patients met criteria for ODD ($\chi^2=85.3$, $df=1$, $p<0.001$). ODD prevalence was similar in either sex regardless of IRR status. ODD was somewhat more dominant in the preadolescent versus the adolescent IRR subset (89.6% vs. 67.9%, $\chi^2=5.65$,

$p=0.017$). The conduct disorder rate (0.6%) was too low to analyze. Table 3 lists these group differences.

In the full sample, the rates of all ADHD subtypes were similar between the boys and the girls. IRR status changed this pattern. The frequency of ADDI was similar in the IRR/NIRR cohorts; there was a trend for higher rates of ADDC (68.6% vs. 58.5%; $\chi^2=3.13$, $df=1$, $p=0.077$) in the IRR group; but now there was a significantly *lower* rate of hyperactive ADHD (ADHD) in the IRR patients (1.9% vs. 8.9%, respectively; $p=0.012$, FE) regardless of sex. However, there were sex differences among the ADHD subtypes according to their IRR status. ADDI was most characteristic of IRR girls ($\chi^2=4.45$, $df=1$, $p=0.035$). So, within the IRR subjects themselves, 51.7% (15/29) of girls and 21.1% (16/76) of boys had ADDI ($\chi^2=8.1$, $df=1$, $p=0.004$). Although the proportional frequency of ADDC did not differ within the IRR/NIRR groups by sex, within the IRR sample alone ($n=105$), boys had a significantly higher rate of ADDC than girls (76.3% [58/76] vs. 48.3% [14/29]; $\chi^2=6.4$, $df=1$, $p=0.011$). To summarize these findings within the IRR dichotomy, IRR girls had the highest rate (51.7%) of ADDI and IRR boys, the lowest rate (21.1%); NIRR boys had the highest rate (10.0%) of ADHD whereas IRR girls had the lowest rate (0.0%); and IRR boys had the highest rate (76.3%) of ADDC while IRR girls had the lowest rate (48.3%). The symptom of IRR appeared to impinge more on the girls' inattention symptomatology and decreased their hyperactive symptoms, while it increased combined symptomatology in boys. (For further delineation of these ADHD rates, see Supplementary Table 3.)

The influence of IRR on symptomatic characteristics was examined within those diagnoses that showed differences between IRR and NIRR cases (i.e., affective, SA, ODD, and ADHD). Simple phobias were not addressed because of the individual specificity of this disorder. Within the affective symptoms, IRR subjects had significantly higher rates of depressed mood ($\chi^2=37.8$, $df=1$, $p<0.001$), fatigue ($\chi^2=10.0$, $df=1$, $p=0.002$), insomnia ($\chi^2=5.68$, $df=1$, $p=0.017$), self-pity ($\chi^2=4.82$, $df=1$, $p=0.028$), hopelessness ($\chi^2=5.78$, $df=1$, $p=0.016$), and negative self-image ($\chi^2=25.8$, $df=1$, $p<0.001$). The separation anxiety symptoms of fears sleeping alone ($\chi^2=7.60$, $df=1$, $p=0.009$) and nightmares ($\chi^2=3.88$, $df=1$, $p=0.049$) were significantly *less* common in the IRR sample. All ODD symptoms were more prevalent in the IRR sample. ADHD symptoms of carelessness ($\chi^2=4.57$, $df=1$, $p=0.032$), difficulty listening ($\chi^2=6.05$, $df=1$, $p=0.014$), and avoids tasks ($\chi^2=6.69$, $df=1$, $p=0.014$) were more frequent in the IRR group.

To identify the most prominent predictors of IRR, the diagnoses and symptoms that on univariate analysis showed a difference between IRR and NIRR subjects were placed into a logistic regression. The first analysis looked at diagnostic and demographic variables as predictors of IRR. A second regression looked at specific symptoms and demographic variables as predictors of IRR.

The logistic regression controlling for age and gender found that IRR was associated with MDD (OR: 33.4; $p<0.001$, CI=4.1-271.7), MDDD (OR: 11.2; $p<0.001$; CI=6.7-18.7), and ODD (OR: 11.6; $p<0.001$, CI=6.6-20.6) but not with AnyAD. IRR youths were more likely to have ADDC (OR: 1.7; $p=0.02$, CI 1.1-2.8) and not ADDI (OR: 0.77; $p=0.29$, CI=0.5-1.3). Irritability was related to higher rates of three ADHD symptoms, six affective symptoms, and eight ODD symptoms. In contrast, IRR was related to lower rates of one SA symptom (fears sleeping alone) with a trend for a second symptom (nightmares). Demographic variables had no effect on symptomatic or diagnostic parameters (Table 4).

4. Discussion

The co-occurrence of depression and ODD with ADHD is not a new finding (Angold et al., 1999; Biederman et al., 1998b). DD is reported more frequently in patients with ADDC (Vance et al., 2005). This data set, however, expands these previous reports because it shows the unique contribution of the symptom of IRR alone within ADHD. The question remains, where does this sample of IRR ADHD children fit within the current bipolar child phenotype presented in the literature. It seems clear that this sample is not related to the bipolar child described in the COBY (Course and Outcome of Bipolar Illness in Youth) study (Axelson et al., 2006; Birmaher et al., 2006), because bipolar children were excluded from this sample. Rather, there are more similarities to the child with severe mood dysregulation (SMD) described by Liebenluft (Brotman et al., 2006; Leibenluft et al., 2003b).

Evidence-based data supporting the predictive validity of SMD and chronic, nonepisodic irritability are based on two epidemiological samples, the Great Smoky Mountain Study (Brotman et al., 2006) and the community-based New York Longitudinal Study (Liebenluft et al., 2006; Stringaris et al., 2009). These studies show that SMD and chronic irritability more likely predict a nonbipolar, depressive disorder outcome. Nonetheless, these studies only provide a proxy validation because they are retrospective analyses not originally designed to look at SMD. The irritable construct analyzed in these studies varied between cohorts and was collated from previously rated symptomatic scores including several symptom overlaps with affective disorders, ADHD, and ODD (Brotman et al., 2006; Liebenluft et al., 2006; Stringaris et al., 2009). These validating studies must also be viewed together with a more recent follow-up of the Great Smoky Mountain Study cohort (Copeland et al., 2009).

This later report controlling for comorbidities analyzed the homotypic and heterotypic predictions of baseline child psychiatric diagnoses into young adulthood. The most consistent finding was that either child or adolescent ODD predicted later depressive disorder. Child overanxious disorder (OAD) also exhibited a heterotypic prediction with depressive disorders but mostly in males. Early onset anxiety disorder predicting adult affective disorder was similarly noted in the New York cohort (Pine et al., 1998). It is of interest that four of seven OAD symptoms are minor depression criteria (Table 1). Because the lifetime rates of anxiety disorders (58.2%) and ODD (84.9%) are high in those with SMD (Leibenluft, 2011), these data suggest that SMD's later prediction of a mood disorder is probably driven by the high comorbid rates of these two disorders and is not unique to the SMD phenotype. The heterotypic continuity of the SMD child suggests that SMD is a vulnerability phenotype for affective disorders. The fact that the SMD phenotype has a unique diagnostic outcome and specific biological parameters compared to the bipolar child supports its differentiation from the bipolar youth (Leibenluft, 2011). Nonetheless, because affective and ODD comorbidities were allowed in the SMD category, it is difficult to know to which diagnostic domain any biological perturbation belongs. Biological deviations are not necessarily diagnosis specific, particularly if there is diagnostic overlap (van Praag, 1997).

This analysis highlights the significance of IRR alone to define a phenotype similar to the SMD child with high rates of ODD and comorbid anxiety disorder. The explanation for the lower rate of anxiety disorders in this cohort compared to those reported in SMD may be that this ADHD sample assessed concurrent rather than lifetime rates. The high rate of concurrent affective disorders (76.2%) puts a somewhat different clinical perspective on these children, because most of the previous studies also reported lifetime prevalence rather than concurrent comorbid depression. These data suggest that IRR mood in the ADHD

population defines a unique concurrent pattern of an irritable affective disorder cooccurring with ODD. The affective symptoms are most consistent with either a minor depressive disorder or dysthymia. Although those with MDD were excluded from this study at the initial screening, pure IRR depression (without depressed mood or pervasive anhedonia) was previously shown highly associated with MDDD and not MDD, in an enriched depressive sample of more than 400 adolescents (Ambrosini et al., 1997).

The affective symptoms in this irritable sample are consistent with DSM V criteria for chronic depressive disorder (CDD) because they share the following symptoms: insomnia, fatigue, low self-esteem/negative image, and hopelessness. CDD also retains the qualifier that in children and adolescents, “mood can be irritable.” The fact that noncomorbid ADHD is essentially devoid of IRR places this clinical constellation most clearly in the affective domain.

The degree of IRR identified in this sample may not appear as severe as those labeled with SMD or the DSM V proposed DMDD because the majority had mild to moderate irritability based on the K-SADS. But even this degree of IRR had major effects on concurrent comorbidity. Within this sample, 76.2% of the IRR group had an affective disorder and 83.8% had ODD. Among the remaining 25 IRR subjects without a depressive disorder, 18 (17.1%) represented the IRR ADHD/ODD child; 4 (3.8%) represented IRR anxiety disorder children; and 3 (2.9%) had only ADHD. Also, the validating studies of SMD were epidemiological cohorts that would have a less intense symptomatic pattern than this current clinical sample.

Because affective symptomatology in these IRR MDDD children is subtle (more subjective than overt) compared to ODD symptoms and IRR itself, clinicians may overlook this affective pattern. In fact, in none of the validating papers on SMD were depressive symptom prevalences reported. Proposed DMDD criteria (American Psychiatric Association, 2011) that represent the SMD phenotype only require one depressive symptom, which is that “nearly every day, mood between temper outbursts is persistently negative (irritable, angry, and/or sad).” Depressive disorders are exclusionary if the temper dysregulation occurs exclusively during an affective illness. The explosion of bipolar diagnoses in youths emerged because clinicians appeared to diagnose ADHD with only the symptom of irritability as bipolar disorder. This finding was not what Biederman's group identified (Wozniak et al., 1995). DMDD criteria in their current form may be proposing an analogous diagnostic schema that minimizes depressive symptomatology and proposes diagnosing an affective disorder with one symptom, namely, negative mood. It might be more parsimonious that this new affective diagnostic grouping be labeled chronic depressive disorder with temper dysregulation. This labeling would then require a depressive symptom complex as seen in CDD. An analogous coding could be applied to those with MDD. Those without an affective disorder are within the irritable ODD/ADHD or anxious domain. This latter subset was almost one-quarter of the IRR subjects in this sample.

DSM IV-TR allows diagnosing children with an affective disorder if IRR is present. Although “pure” IRR affective disorder is only 8.4% of this sample, the children identified in this analysis appeared to have an irritable affective disorder with a distinct comorbid pattern. This diagnostic cluster clearly can be populated with those exhibiting variable severity as is apparent in MDD or in other diagnostic domains. A new diagnosis of DMDD may not be warranted because of its possible similarity to CDD until further clarity is available on the depressive symptom prevalence in DMDD. Clearly, the symptom of irritability is a potent mediator of ODD and MDDD within this ADHD sample. The predictive validity of this IRR depressive subtype remains to be seen, although the early finding of SMD/chronic irritability supports its depressive classification since it more likely

predicts a later affective disorder than a bipolar outcome (Brotman et al., 2006, Stringaris et al., 2012). Its relationship to anger attacks in adults (Fava and Rosenbaum, 1999) with depression or intermittent explosive disorder (Coccaro, 2010) is also unclear.

This analysis is limited because it was from one clinical service that excluded presumed bipolar or major depressive subjects. Since this sample only included Caucasian ADHD children, the findings could be considered cohort specific; but, the Great Smoky Mountain Study also was predominately Caucasian youths (Brotman et al., 2006). Nonetheless, this ADHD sample's clinical characteristics closely resemble other outpatient groups, placing it within the overall ADHD domain (Elia et al., 2008). It may be that IRR has differing effects within other diagnostic groups. The young mean age of the sample (10.2 years; 78.6% <13 years old) does restrict the comorbid pattern with disorders having a later age of onset, but older age would only tend to increase the prevalence of affective disorders (Costello et al., 2003). In a longitudinal follow-up study averaging 7 years, Biederman et al. (2009) noted that ADHD was a risk factor for a bipolar switch in those with a lifetime diagnosis of a unipolar depressive disorder. This does suggest that some of the ADHD depressives identified in this study could eventually exhibit a bipolar outcome. However, Biederman's samples did not exclude bipolarity and depression at baseline, which was an entry criterion for this current study.

6. Conclusions

This analysis clearly shows that irritability among children with ADHD is a potent symptom increasing comorbidity. It preferentially defines a cohort of affectively ill ADHD youth with predominantly comorbid behavioral symptoms. IRR does not act alone but appears intimately associated with temper tantrums and oppositionality to generate an affective diathesis. The finding that IRR is predictive of a concurrent affective disorder complements the predictive validity of this symptom to identify later affective disorders in young adulthood (Copeland et al., 2009; Moreno et al., 2007). It appears imperative to assess the ADHD child with irritability for low-grade affective disorders and conversely, the irritable child for affective illness. The symptomatology of RDC, defined minor depression, and DSM IIR criteria for OAD appear relevant to this debate. It remains a heuristic question whether DMDD should be incorporated as a new affective diagnosis or alternately classified as a subtype of chronic depressive disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Role of the funding source:

Funding for this study was provided in part by the National Institute of Mental Health (K23MH066275-01) to Dr. Elia. The funding source played no role in the study design, collection, analysis and interpretation of data, writing of the report or in the decision to submit the paper for publication.

References

- Ambrosini, P.J.; Myers, G.M.; Bianchi, M.D.; Metz, C. Irritable and depressed mood: Are they synonymous?; Paper presented at the 150th Annual Meeting of the American Psychiatric Association; San Diego, CA. 1997.
- American Psychiatric Association. [March 6, 2012] DSM-5 Development: D 00 Disruptive Mood Dysregulation Disorder. 2011. Available at: <http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=397>.

- Angold A, Costello EJ, Erkanli A. Comorbidity. *J. Child Psychol. Psychiatry.* 1999; 40:57–87. [PubMed: 10102726]
- Angold A, Costello EJ, Worthman CM. Puberty and depression: the roles of age, pubertal status and pubertal timing. *Psychol. Med.* 1998; 28:51–61. [PubMed: 9483683]
- Axelson D, Birmaher B, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Bridge J, Keller M. Phenomenology of children and adolescents with bipolar spectrum disorders. *Arch. Gen. Psychiatry.* 2006; 63:1139–1148. [PubMed: 17015816]
- Biederman J, Klein RG, Pine DS, Klein DF. Resolved: mania is mistaken for ADHD in prepubertal children [see comments]. *J. Am. Acad. Child Adolesc. Psychiatry.* 1998a; 37:1091–1096. discussion 1096-1099. [PubMed: 9785721]
- Biederman J, Mick E, Faraone SV. Depression in attention deficit hyperactivity disorder (ADHD) children: “true” depression or demoralization? *J. Affect. Disord.* 1998b; 47:113–122. [PubMed: 9476751]
- Biederman J, Petty CR, Byrne D, Wong P, Wozniak J, Faraone SV. Risk for switch from unipolar to bipolar disorder in youth with ADHD: a long term prospective controlled study. *J. Affect. Disord.* 2009; 119:16–21. [PubMed: 19324422]
- Birmaher B, Axelson D, Strober M, Gill MK, Valeri S, Chiappetta L, Ryan N, Leonard H, Hunt J, Iyengar S, Keller M. Clinical course of children and adolescents with bipolar spectrum disorders. *Arch. Gen. Psychiatry.* 2006; 63:175–183. [PubMed: 16461861]
- Blader JC, Carlson GA. Increased rates of bipolar disorder diagnoses among U.S. child, adolescent, and adult inpatients, 1996-2004. *Biol. Psychiatry.* 2007; 62:107–114. [PubMed: 17306773]
- Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, Leibenluft E. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol. Psychiatry.* 2006; 60:991–997. [PubMed: 17056393]
- Carlson GA. Mania and ADHD: comorbidity or confusion. *J. Affect. Disord.* 1998; 51:177–187. [PubMed: 10743850]
- Carlson GA. Who are the children with severe mood dysregulation, a.k.a. “rages”? *Am. J. Psychiatry.* 2007; 164:1140–1142. [PubMed: 17671272]
- Chang FM, Kidd JR, Livak KJ, Pakstis AJ, Kidd KK. The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Hum. Genet.* 1996; 98:91–101. [PubMed: 8682515]
- Coccaro EF. Intermittent explosive disorder: development of integrated research criteria for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. *Compr. Psychiatry.* 2010; 52:119–125. [PubMed: 21295216]
- Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch. Gen. Psychiatry.* 2009; 66:764–772. [PubMed: 19581568]
- Costello EJ, Mustillo S, Erkanli A, Keeler G, Angold A. Prevalence and development of psychiatric disorders in childhood and adolescence. *Arch. Gen. Psychiatry.* 2003; 60:837–844. [PubMed: 12912767]
- Elia J, Ambrosini P, Berrettini W. ADHD characteristics: I. Concurrent co-morbidity patterns in children & adolescents. *Child. Adolesc. Psychiatry. Ment. Health.* 2008; 2:15. [PubMed: 18598351]
- Fava M, Rosenbaum JF. Anger attacks in patients with depression. *J. Clin. Psychiatry.* 1999; 60(Suppl 15):21–24. [PubMed: 10418810]
- Kowatch RA, Fristad M, Birmaher B, Wagner KD, Findling RL, Hellander M. Treatment guidelines for children and adolescents with bipolar disorder. *J. Am. Acad. Child. Adolesc. Psychiatry.* 2005; 44:213–235. [PubMed: 15725966]
- Leibenluft E. Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *Am. J. Psychiatry.* 2011; 168:129–142. [PubMed: 21123313]
- Leibenluft E, Blair RJ, Charney DS, Pine DS. Irritability in pediatric mania and other childhood psychopathology. *Ann. N. Y. Acad. Sci.* 2003a; 1008:201–218. [PubMed: 14998886]
- Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. *Am. J. Psychiatry.* 2003b; 160:430–437. [PubMed: 12611821]

- Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic versus episodic irritability in youth: a community-based, longitudinal study of clinical and diagnostic associations. *J. Child. Adolesc. Psychopharmacol.* 2006; 16:456–466. [PubMed: 16958570]
- McClellan J. Commentary: treatment guidelines for child and adolescent bipolar disorder. *J. Am. Acad. Child. Adolesc. Psychiatry.* 2005; 2005; 44:236–239. [PubMed: 15725967]
- Mick E, Spencer T, Wozniak J, Biederman J. Heterogeneity of irritability in attention-deficit/hyperactivity disorder subjects with and without mood disorders. *Biol. Psychiatry.* 2005; 58:576–582. [PubMed: 16084859]
- Moreno C, Laje G, Blanco C, Jiang H, Schmidt AB, Olfson M. National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Arch. Gen. Psychiatry.* 2007; 64:1032–1039. [PubMed: 17768268]
- Pine DS, Cohen P, Gurley D, Brook J, Ma Y. The risk for early-adulthood anxiety and depressive disorders in adolescents with anxiety and depressive disorders. *Arch. Gen. Psychiatry.* 1998; 55:56–64. [PubMed: 9435761]
- Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch. Gen. Psychiatry.* 1978; 35:773–782. [PubMed: 655775]
- Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. *Am. J. Psychiatry.* 2009; 166:1048–1054. [PubMed: 19570932]
- Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: phenotypic associations and genetic links with depressed mood. *Am. J. Psychiatry.* 2012; 169:47–54. [PubMed: 22193524]
- van Praag HM. Over the mainstream: diagnostic requirements for biological psychiatric research. *Psychiatry. Res.* 1997; 72:201–212. [PubMed: 9406910]
- Vance A, Sanders M, Arduca Y. Dysthymic disorder contributes to oppositional defiant behaviour in children with Attention Deficit Hyperactivity Disorder, combined type (ADHD-CT). *J. Affect. Disord.* 2005; 86:329–333. [PubMed: 15935256]
- Wozniak J, Biederman J, Kiely K, Ablon JS, Faraone SV, Mundy E, Mennin D. Mania-like symptoms suggestive of childhood-onset bipolar disorder in clinically referred children. *J. Am. Acad. Child. Adolesc. Psychiatry.* 1995; 34:867–876. [PubMed: 7649957]

Fig. 1. Distribution of affective disorders: Irritable (IRR) (n=105) sample compared with nonirritable (NIRR) (n=395) sample of ADHD patients. MDD=major depressive disorder; IMDD=irritable MDD; MD=minor depression; IMD=irritable MD; DD=dysthymic disorder; IDD=irritable DD; Cyclo=cyclothymic disorder; MDDT= MDD + IMDD; MDDD=MD + IMD + DD + IDD; AnyDD=any depressive disorder. All frequency differences are significant (*p <0.05; **p<0.001).

Table 1

Criteria of minor depression.

Criterion	Minor depression (RDC)	Dysthymic disorder (DSM IVTR)	Overanxious disorder (DSM III/IIIR)
Dysphoric mood	+	+	
Two or more of the following:	+	+	na
Decrease/increase appetite or weight loss/gain	+	+	
Sleep difficulty or excess sleep	+	+	
Loss of energy/fatigue	+	+	
Psychomotor agitation/retardation	+		
Loss of interest/pleasure	+		
Self-reproach/excessive guilt	+		
Difficulty concentrating/indecisive	+	+	
Suicidal ideation/behavior	+		
Tearfulness or sad facies	+		
Pessimistic attitude (hopeless/helpless)	+	+	
Brooding	+		+
Feeling inadequate (negative self-image)	+	+	+
Resentful, irritable, angry, complaining	+		
Demanding/clinging (excessive reassurance)	+		+
Self-pity	+		
Excessive somatization (aches and pains)	+		+
Duration	1 wk for probable; 2 wk for definite	1y, child; 2y, adult	6 months
Not meet criteria for other mood disorders	+	variable	na
May be superimposed on other nonaffective disorders	+	+	na
Impairment at home, work or in social situations	+	+	+

DSM III/IIIR=*Diagnostic and Statistical Manual of Mental Disorders*, 3rd Edition Revised; DSM IVTR=*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision; na=not applicable; RDC=research diagnostic criteria.

Table 2

Demographic characteristics of the ADHD sample.

	Male n (%)	Female n (%)	Total n (%)	Test statistics
Demographic Characteristics				
N (%)	367 (73.4)	133 (26.6)	500	
Age, y (SD)	10.0 (3.1)	10.9 (3.4)	10.2 (3.2)	F=7.44, df=1
Range, y	6.0-18.9	6.1-17.8		p=0.007
Prepub	298 (81.2)	95 (71.4)	393 (78.6)	$\chi^2=4.98$, df=1
Adol	69 (18.8)	38 (28.6)	107 (21.4)	p=0.026
Clinical Characteristics				
IRR	76/367 (20.7)	29/133 (21.8)	105/500 (21.0)	ns
NIRR	291/367 (79.3)	104/133 (78.2)	395/500 (79.0)	
Prepub	59/298 (19.8)	18/95 (18.9)	77/393 (19.6)	ns
Adol	17/69 (24.6)	11/38 (28.9)	28/107 (26.2)	

ADHD=attention deficit hyperactivity disorder; Adol=adolescent, 13 y; IRR=irritable; NIRR=nonirritable; ns=not significant; Prepub=prepubertal, <13 y.

Table 3

Anxiety and behavior disorder frequency by sex in IRR and NIRR ADHD Sample

	Total % (n=500)	IRR % (n=105)	NIRR % (n=395)	Significance
SA	6.2 (31)	3.8 (4)	6.8 (27)	ns
Male	4.1 (15)	3.9 (3)	4.1 (12)	
Female	12.0 (16)	3.4 (1)	14.4 (15)	
Significance	$\chi^2=9.3, df=1$ p<0.002	ns	$\chi^2=11.2, df=1$ p<0.001	
AnyAD	29.0 (145)	34.3 (36)	27.5 (109)	ns
Male	25.9 (95)	27.6 (21)	25.4 (74)	
Female	37.6 (50)	51.7 (15)	33.7 (35)	
Significance	$\chi^2=5.9, df=1$ p<0.015	$\chi^2=4.4, df=1$ p<0.036	ns	
ODD	43.6 (218)	83.8 (88)	32.9 (130)	$\chi^2=85.3, df=1$ p<0.001
Male	44.4 (163)	88.2 (67)	33.0 (96)	
Female	41.4 (55)	72.4 (21)	32.7 (34)	
Significance	ns	ns	ns	

ADHD=attention deficit hyperactivity disorder; AnyAD=any anxiety disorder; IRR=irritable mood; NIRR=nonirritable; ns=nonsignificant; ODD=oppositional defiant disorder; SA=separation anxiety.

Table 4

Odds ratio of symptoms as a function of irritability, controlling for age and gender

	Odds ratio	p Value	95% Confidence interval
Attention deficit hyperactivity disorder			
Difficulty listening	11.00	.019	1.48–82.03
Careless	3.08	.036	1.08–8.80
Avoids tasks	2.56	.017	1.18–5.52
Affective Disorder			
Depressed mood	4.42	<.001	2.68–7.29
Negative self-image	3.26	<.001	2.05–5.18
Hopelessness	2.50	.020	1.15–5.43
Self-pity	2.05	.026	1.09–3.86
Fatigue	1.91	.005	1.22–3.00
Insomnia	1.71	.018	1.10–2.65
Separation anxiety			
Fears sleeping alone	0.49	.032	.26–.94
Nightmares	0.28	.083	.06–1.19
Opposition defiant disorder			
Temper tantrums	6.63	<.001	4.02–10.93
Argumentative	6.44	<.001	3.33–12.44
Easily annoyed	4.48	<.001	2.80–7.17
Spiteful	4.04	<.001	2.43–6.71
Blames others	3.79	<.001	2.34–6.15
Easily angered	3.32	<.001	2.11–5.21
Provokes others	3.11	<.001	2.98–5.21
Defiant	3.11	<.001	1.98–4.87