Juvenile Bipolar Research Foundation

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The Core Phenotype: Identification of a behavioral marker comprised of aggressive obsessions, anxiety symptoms, and overt aggressive behaviors in youth diagnosed with juvenile-onset bipolar disorder.

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Background

Aggressive behavior is a characteristic element of several forms of childhood psychopathology and a primary behavioral symptom bringing children to medical attention. Clinical experience with juvenile-onset bipolar disorder suggests that worries about harm to self or important others are intense and recurrent in this condition, and are especially prominent in children or adolescents who engage in self-harm behaviors and/or physically and verbally aggressive behaviors. The current debate about the cardinal features of juvenile mania and its differentiation from other psychiatric disorders, in attempting to refine the operational definitions of pediatric bipolar disorder, has appropriately placed strong emphasis on the importance of aggression and its relationship to anxiety and paranoia (Liebenluft et al, 2003).

The Core Phenotype is a set of diagnostic criteria for pediatric bipolar disorder that includes both a categorical definition of mania and dimensional features, including fear of harm, overt aggressive behavior, and a low threshold for anxiety that are, in our view, pathognomonic of bipolar disorder in children. Our primary objective in the study reported here was to inquire whether children with a past or present clinical diagnosis of bipolar disorder, identified by their parents/guardians as being quite fearful of harm, were also more behaviorally aggressive. We expected scores on The Child Bipolar Questionnaire (CBQ), a screening inventory that includes 33 core items (Core Diagnostic Criteria) used to identify the Core phenotype, to be strongly correlated with measurable indices of aggressive obsessions, anxiety, and overt aggressive behaviors in adolescents and children at risk for or diagnosed with bipolar disorder.

Methods

Sample selection for the study group from whom data summarized in this report were obtained was based on two factors: [1] parental report that the child/adolescent had been diagnosed with bipolar disorder, either currently or at some prior time; and [2] a score > 40 on the Child Bipolar Questionnaire (CBQ). Via a secure, internet-based data acquisition system established and maintained by the Juvenile Bipolar Research Foundation (JBRF), parents/guardians completed the CBQ, the Yale-Brown Obsessive-Compulsive Scale (YBOCS), and the Overt Aggression Scale (OAS). A fear-of-harm index was calculated by summing 6 YBOCS items occurring at a frequency of "2" ("sometimes") or higher:

[1] Fear might harm self
[2] Fear might harm others
[3] Fear harm might come to self
[4] Fear harm will come to others (may be because of something child did or did not do)
[5] Fear will act on unwanted impulses (e.g., to stab a family member)
[6] Fear will be responsible for something else terrible happening (e.g., fire, burglary, flood)

Fear-of-harm high and low subgroups based on median split were compared on OAS subscales and OAS total score, as well as on the two most severe OAS items:

[11] Mutilates self, causes deep cuts, bites that bleed, internal injury, fracture, loss of consciousness, loss of teeth
[15] Attacks others, causing severe physical injury (broken bones, deep lacerations, internal injury)

Subjects scoring at high and low on the fear-of-harm index were then compared on OAS and YBOCS total scores and on mean CBQ Core Criteria scores.

Results

There were 819 subjects for whom both YBOCS and OAS data were obtained via the JBRF internet-based system. For 603 (73.6%) of these subjects, it was reported that a diagnosis of bipolar disorder had formally been assigned by a clinician (i.e., child psychiatrist, psychiatrist, pediatrician, or other clinician). Age, sex, number of psychotropic medications, and number of psychiatric diagnoses in fear of harm high vs. low subgroups are summarized in Table 1. There was a very large difference between the two fear-of-harm subgroups on average OAS total score (11.7 ± 3.3 vs. 8.41 ± 4.8), with a difference at the mean of more than 39% (Table 1).

Summary data on the most severe OAS item measures of harms-self (item 11) and harms-others (item 15) are provided in Table 2. The fear-of-harm median split was significantly positively correlated with positive responses to both OAS Item 11 (harms-self) and OAS Item 15 (harms-others), with risk ratios of 3.06 (95%CI 1.59-5.89) and 30.4 (4.13 – 224), respectively. These data indicate that children/adolescents identified as having high fear-of-harm anxieties were 3-fold (RR = 3.06) more likely to be identified by their parents as engaging in severely self-injurious behaviors than subjects with relatively low fear-of-harm anxieties; and these same children were 30-fold (RR = 30.4) more likely to be identified as engaging in severely injurious assaults on others. Older children were more likely to be identified by their parents/guardians as engaging in very severe self-harm behaviors, but younger children were more likely to be identified as engaging in severe harm-to-others behaviors.

The six YBOCS fear-of-harm items very strongly separate children and adolescents who were/were not identified by their parents/guardians as actively engaging in severe harm-to-others behaviors. This is illustrated graphically in Figure 1, which shows the count of the number of YBOCS fear-of-harm items endorsed by parents in relation to whether the child was/was not identified as exhibiting severe harm-to-others behaviors on OAS Item 15. The figure shows a very clear separation between subjects with/without overt harm-to-others behavioral patterns. For example, among the 25 subjects with a "Yes" response to OAS Item 15, more than one-fourth (28.0%) had a positive response on all six of the YBOCS fear-of-harm items; whereas, among subjects scored "No" on OAS Item 15, this percentage was 8.8%.

In a small (N=33) healthy comparison group, these fear-of-harm – overt aggressive behavior correlations were near-zero.

The comparisons of fear of harm subgroups and their scores on Core phenotype criteria as well as on well-validated measures of anxiety and aggression are summarized in Table 3. With a range of possible scores from 0 to 6, the fear-of-harm index averaged 2.38 + 2.0 (median = 2.0). High vs. Low subgroups based on the fear-of-harm index (median split) had substantially different YBOCS, OAS, and CBQ Core Criteria scores. The YBOCS difference between these two subgroups was by construction, because the fear-of-harm high vs. low subgroups were defined in terms of YBOCS item scores. The other two contrasts were highly statistically significant (z= 9.45 and, z = 8.57, respectively, both p<0.001).

Conclusions

The linkage of fear of harm to aggressive behavior in this sample of children with a community diagnosis of bipolar disorder may indicate that fear of harm is an important dimension of the condition with potential utility in differential diagnosis. The robust relationship between CBQ Core Criteria and well-validated indices of fear of harm, anxiety, and overt aggressive behavior supports the existence of a distinct phenotype that includes cardinal symptoms from overlapping DSM-IV categories such as anxiety disorders and disruptive behavior disorders, as well as primary symptoms of juvenile mania.

References

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Table 1.

High vs. low fear-of-harm subgroups: study sample characteristics

Measure[a]	Fear-of-Harm High	Fear-of-Harm Low	x^2 or z [b]	p
Number (%)	266 (44.1)	337 (55.9)	----	----
Males (N, %)	184/266 (69.2)	213/337 (63.2)	2.35	0.12
Age (years)	10.5 ± 3.7 (2-20)	11.2 ± 3.5 (2-20)	–2.39	0.017
No. psychotropic medicines	2.26 ± 1.7 (0-18)	2.20 ± 1.4 (0-10)	0.48	0.63
No. psychiatric diagnoses	3.21 ± 2.0 (0-9)	2.73 ± 1.8 (0-9)	3.08	0.002
YBOCS total score [c]	22.7 ± 10.9 (4-36)	14.1 ± 13.2 (0-36)	----	----
OAS total score	11.7 ± 3.3 (0-15)	8.41 ± 4.8 (0-15)	9.93	<0.001

a. Reported are number (N) and percentage (%) for binary measures, and mean ± SD (range) for continuous data.
b. Degrees of freedom (df) = 1 for x^2.
c. Statistical significance of high vs. low Fear-of-Harm subgroup differences on the YBOCS total score was not examined because scores on a subset of the YBOCS scale were used to define the Fear-of-Harm subgroups.

Table 2.

Characteristics of children reported by parents as Yes and No on Overt Aggression Scale items indicating severe symptoms of (A) self-harm or (B) attacks on other persons

Measure[a]	Yes on OAS item	No on OAS item	Risk[b] Ratio	(95%CI)[b]	z	p
A. OAS Item 11 (self-harm) [c]						
Number (%)	41 (6.8)	562 (93.2)	----	----	----	---
Males	27/41 (65.8)	370/562 (65.8)	1.00	0.55-1.87	0.00	0.99
Age > 10 years	29/41 (70.7)	306/558 (54.8)	1.90	1.00-3.66	1.96	0.049
Fear-of-harm >median	29/41 (70.7)	237/562 (42.2)	3.06	1.59-5.89	3.35	0.001
B. OAS Item 15 (harm to others) [d]						
Number (%)	25 (4.2)	578 (95.8)	----	----	----	---
Males	19/25 (76.0)	378/578 (65.4)	1.64	0.67-4.05	1.08	0.28
Age > 10 years	8/25 (32.0)	327/574 (57.0)	0.37	0.16-0.85	–2.36	0.018
Fear-of-harm >median	24/25 (96.0)	242/578 (41.9)	30.4	4.13-224	3.35	0.001

a. Fear-of-Harm High vs. Low subgroups defined by median split on 6 YBOCS "fear-of-harm" items, together with YBOCS frequency ratings of at least 2 (sometimes) on each of these 6 items.
b. Risk ratio and 95%CI estimated using generalized linear modeling (GLM) methods.
c. OAS Item 11: Mutilates self, causes deep cuts/bites that bleed, internal injury, fracture, loss of consciousness, loss of teeth. Current behavior rated Yes/No by parents/guardians.
d. OAS Item 15: Attacks others, causing severe physical injury (broken bones, deep lacerations, internal injury) mutilates self, causes deep cuts/bites that bleed, internal injury, fracture, loss of consciousness; rated Yes/No.

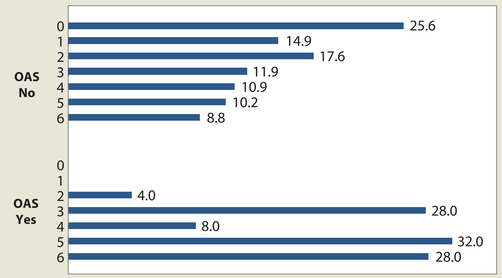
Table 3.

High vs. low fear-of-harm subgroups: scores on the YBOCS and OAS scales, and on the CBQ Core subscale

Measure [a]	Fear-of-Harm High	Fear-of-Harm Low	z[b]	p
Number (%)	266 (44.1)	337 (55.9)	----	----
YBOCS Current (N=603) [c]	22.7 ± 10.9	14.1 ± 13.2	----	----
OAS total score (N=599)	11.7 ± 3.3 (0-15)	8.41 ± 4.8 (0-15)	9.93	<0.001
CBQ Core subscale (N=597)	27.3 ± 4.4 (9-33)	23.5 ± 5.9 (4-33)	8.57	<0.001

a. Reported are mean ± SD (range) for continuous data.
b. Z-statistic estimated using linear regression modeling methods, with adjustment for age and sex.
c. Statistical significance of high vs. low Fear-of-Harm subgroup differences on the YBOCS total score was not examined because scores on a subset of the YBOCS scale were used to define the Fear-of-Harm subgroups.

Figure 1.
YBOCS Fear of Harm by OAS Severe Attacks on Others



Percent of All Subjects Scoring 0-6 on Fear of Harm Index