Is this child bipolar? What's needed to improve diagnosis

With genetic and brain imaging biomarkers, early intervention could protect at-risk kids

When does bipolar disorder begin? That question confounds clinicians, worries parents, and is leading researchers such as Kiki D. Chang, MD, to look for answers in families with this highly heritable disorder.

"Parents with bipolar disorder know what's happening if their children have early symptoms," Dr. Chang says. "They tell me, 'I don't want my child to go through what I went through, and he's having the same symptoms I did.'"

Dr. Chang believes early psychotherapy and medication might prevent prodromal bipolar disorder from fully developing. His team at Stanford University is among those seeking genetic and brain imaging biomarkers to make a pediatric bipolar diagnosis more reliable. Lack of age-specific criteria may be causing overdiagnosis, as suggested by a 40-fold increase in 10 years in the number of children and adolescents being treated for bipolar disorder.[1]

In this interview by Robert A. Kowatch, MD, PhD, Dr. Chang describes a child with probable early signs of bipolar disorder and discusses why early intervention is both complicated and promising.

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Children at risk for bipolarity

DR. KOWATCH: You're studying children considered at high risk for developing bipolar disorder; why are these studies important?

DR. CHANG: High-risk children represent a chance to understand risk factors for developing bipolar disorder and what the early symptoms are. By "high risk," we mean children and adolescents who possess a genetic predisposition toward bipolar disorder.

Bipolar disorder develops over time; a boy such as "Brian" (***Box 1, page 24***) likely would have gone 3 to 5 years on the stimulant—not doing well—until he had a manic episode at age 14 or 15. The full mood episode usually does not develop until later, with the right—or you could say wrong—combination of environment and stressors acting on a genetic predisposition.

DR. KOWATCH: Do the parents of the children you're studying have bipolar disorder?

continued

Clinical Point

Once a battery of biomarkers has been put together, the more certain the diagnosis of bipolar disorder will become

Box 1

Case report: 10-year-old is 'just like I was,' says bipolar mom

Mrs. M, age 35, had early-onset depression but was not diagnosed with bipolar disorder until age 22. She requests a consultation for her 10-year-old son, Brian, whom she suspects also may have bipolar disorder. "I know there's something going on; he's just like I was, but no one would listen to me," she says.

The boy's pediatrician prescribed methylphenidate for "a little inattention" but felt that Brian was doing okay in school and had some friends. The stimulant might be helping, says Mrs. M, but she is not sure.

You talk to Brian and learn he has some anxiety. He sometimes gets very excited and runs around, and sometimes he does not sleep well. If you consider all the symptoms, this child has anxiety, attention-deficit/hyperactivity disorder, short depressive periods that affect his functioning, and a parent with bipolar disorder.

You ask further, and Brian tells you about hearing conversations and voices of old friends, his parents, and unknown people in his head, usually neutral, and not commanding or commentating. No one has asked him about parapsychotic phenomena, and he's never reported this to anyone.

Clinical Point

Our goal is to stop 'kindling': to prevent environmental or developmental 'sparks' from interacting with genetic predisposition

DR. CHANG: Yes; we're studying what we call "bipolar offspring"—children with biological parents with bipolar disorder (*Box 2, page 31*).[2-4] One also could look at siblings; having a brother or sister with bipolar disorder increases risk as well. If you search back in these families, usually you'll find many relatives with bipolar disorder who reflect the child's genetic predisposition.

'Kindling' in bipolar disorder

DR. KOWATCH: What have you seen in children whose parents have bipolar disorder?

DR. CHANG: We've tracked more than 200 bipolar offspring for up to 10 years. In some families we've seen the natural progression toward full mania and bipolar disorder.

We've also seen children who start to show symptoms but don't develop full bipolar disorder. These children have had clinical treatment, so we're not sure if the intervention prevented full bipolar disorder or if they would not have developed it anyway. Some children have developed mood symptoms and other psychiatric problems that have resolved with early intervention.

DR. KOWATCH: How is "kindling" related to early-onset bipolar disorder?

DR. CHANG: Kindling, which originally referred to seizure disorders, also has been applied to affective disorders.[5] Early stressors and triggers appear to add up over time and combine with genetic predisposition to create a full mood episode. After that break, it becomes easier and easier to have the next episode, and the disorder becomes chronic and more difficult to treat.

The goal of our work is to stop kindling in bipolar disorder—to prevent environmental or developmental "sparks" from interacting with genetic predisposition and igniting a chronic, spontaneous course of mood episodes.

Brain imaging biomarkers

DR. KOWATCH: Are researchers finding biomarkers for bipolar disorder?

DR. CHANG: The field is young but light-years ahead of where we were 10 years ago. Brain imaging has revealed consistently abnormal areas in children with bipolar disorder. These abnormalities are seen in adults with bipolar disorder as well, but chronic illness, substance abuse, and medication exposure affect the findings in adults. Children have had less exposure to these confounding variables.

We and other groups have identified areas of the prefrontal cortex, amygdala, cerebellum, and striatum that could represent biomarkers, although I wouldn't say yet that there are any markers per se. A decrease in amygdala volume has been found consistently in children with bipolar disorder, for example, but it's not specific

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to bipolar disorder. So we have a way to go before we find specific biomarkers.

In the future, clinicians will probably use a set of 10 to 20 biomarkers, and the more biomarkers a patient has, the greater the risk for bipolar disorder. Once a battery of biomarkers has been put together, the more certain a bipolar disorder diagnosis will become.

Genetic biomarkers

DR. KOWATCH: We've talked about high-risk families; are there genetic markers for bipolar disorder?

DR. CHANG: Like imaging biomarkers, genetic biomarkers for bipolar disorder are likely to be used in combination in the future. We and other groups are studying candidates such as the serotonin transporter gene,[6] brain-derived neurotrophic growth factor,[7] and catechol *O*-methyltransferase (COMT)[8]—and finding that these agents probably are involved.

If you look at common polymorphisms in a set of genes, eventually you'll be able to calculate the risk that a person will develop bipolar disorder. We're also investigating whether genes control the age of onset.

DR. KOWATCH: How are you looking for genetic markers in the high-risk children you're studying?

DR. CHANG: We start with the proband—the child of a bipolar parent—and then study as much of the family as we can. Approximately 50% of the probands' first- or second-degree relatives have a mood disorder—so our samples are highly loaded.

We're interested in the interaction between genes and brain function and structure: How do genetic predispositions lead to brain differences that create vulnerability for mood disorders—in this case, bipolar disorder?

To explore that question, we're starting a 5-year study funded by the National Institutes of Health (NIH). We're recruiting 50 sibling pairs in which 1 child has early bipolar symptoms and the other is healthy. We will compare these pairs' genetic and brain imaging profiles with those of 30 healthy children with no genetic risk for bipolar disorder, as far as we can tell.

Something makes 1 child develop bipolar disorder and another child not. By matching siblings with shared environments, we're trying to eliminate environmental factors and look at their genetic and brain function differences. We'll use functional brain imaging to look at how children respond to mood-related tasks and standard tasks involving facial emotion exposure to activate brain areas bipolar disorder is thought to affect.

Preventing bipolar 'kindling'

DR. KOWATCH: What interventions might interrupt kindling and help prevent bipolar I disorder from developing in high risk children?

DR. CHANG: Families affected by bipolar disorder are characterized by stress and high expressed emotion; they tend to fight a lot, and we're trying to improve communication and their ability to work together.

continued

Box 2

'Bipolar offspring': High risk for bipolar disorder

In adults, the incidence of bipolar types I and II is approximately 4%.[1] Because two-thirds of adults with bipolar disorder have onset during childhood or adolescence, the incidence of pediatric bipolar disorder may be 1% to 2%. It could be as high as 3% if you include children with prodromes or early forms of the disorder.

The risk of a child developing a bipolar disorder is probably 15% to 20% when 1 biological parent—or sibling—has a bipolar disorder.[2] If both parents have bipolar disorder, some older studies suggest that the child's risk of developing at least a mood disorder would be up to 75%,[3] and depression in a child might develop into a bipolar disorder.

Therefore, the risk of bipolar disorder developing in a child whose parents both have bipolar disorder may be >50% and could approach 75%.

Clinical Point

We think reduced stress—such as from improved family communication and cooperation—could halt the progression of bipolar disorder in at-risk children

Clinical Point

Data point to 2 related but separate pathways to bipolar disorder: early-onset depression—which increases the risk for later mania—and early ADHD

Box 3

Early data: Can medications prevent bipolar disorder?

A 12-week, open-label study of valproate[8] showed symptom improvement in 18 of 23 (78%) children ages 6 to 18 with mood or behavioral symptoms and at least 1 parent with bipolar disorder. On the other hand, a double-blind, controlled trial found no difference in mood symptom changes in 56 children receiving valproate or placebo for up to 5 years. Children in this study were ages 5 to 17, met DSM-IV-TR criteria for cyclothymia or bipolar disorder not otherwise specified, and had at least 1 biological parent with bipolar disorder.[9]

A small, open-label, 12-week prospective study suggested that quetiapine may be useful for treating mood symptoms in adolescents with at least 1 first-degree relative with bipolar disorder. The 20 adolescents (ages 12 to 18) had mood disorder diagnoses but did not meet DSM-IV-TR criteria for bipolar I disorder.[10]

We think reduced stress could halt the progression of the disorder in at-risk children.

Our group is collaborating with Dr. David Miklowitz at the University of Colorado to develop a family psychotherapy program for children who have at least 1 parent or sibling with bipolar disorder and are showing early bipolar symptoms. In a 3-year, NIH-funded treatment development study, 40 children will be randomly assigned to receive 12 sessions of weekly family-focused therapy (FFT) or treatment as usual.

FFT was developed for adolescents already diagnosed with bipolar disorder, and this study will use a modified FFT. Our goals are to help these families understand bipolar disorder, improve family communication, and teach them how to solve problems. We hope to decrease the child's symptoms, improve functioning, and delay or prevent onset to a full manic episode.

We also think some medications have potential for protecting the brain against the progression of bipolar disorder. In vitro evidence exists for lithium, valproate, and carbamazepine to some extent, other anticonvulsants such as lamotrigine, and atypical antipsychotics such as quetiapine and olanzapine. A few preliminary clinical trials have been conducted (*Box 3*)[9-11] but no longitudinal studies.

Recommendations

DR. KOWATCH: What do you recommend that psychiatrists do to help children at risk for bipolar disorder?

DR. CHANG: Ask your adult patients with bipolar disorder how their children are doing. If a child is not doing well, consider referral to a child and adolescent psychiatrist or take an interest yourself and assess the child for early signs of bipolar disorder.

DR. KOWATCH: What are the prodromal symptoms in children and adolescents?

DR. CHANG: In the past, the earliest reported symptoms were thought to include extreme hyperactivity, inappropriate sexuality, and severe depression at a very young age (preschool or school age children). Now data point to 2 major pathways toward bipolar disorder:

- early-onset depression, which elevates risk for later mania
- early attention-deficit/hyperactivity disorder (ADHD).

We see those as related but separate pathways to a similar disorder—or sometimes slightly separate disorders—within the bipolar spectrum.

DR. KOWATCH: So you've got a group with depression and a group with severe ADHD that might develop into bipolar disorder?

DR. CHANG: The ADHD need not be severe. In these children, ADHD may reflect an underlying brain development trajectory toward mood dysregulation. We've also seen anxiety as an initial condition. A cross-sectional study found anxiety to be prevalent in bipolar offspring and a possible risk factor for later mania.[12]

Anxiety is very common in children, so it's hard to tell if it's a precursor for bipolar disorder in an individual child. But looking back, a lot of children who develop bipolar disorder had early anxiety, which may be a marker

Related Resources

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• Chang KD, Gallelli KA. Bipolar disorders and genetics: clinical implications of high heritability. *Medscape Psychiatry & Mental Health* 2004;9(2). Available at: http://www.medscape.com/viewarticle/489331.

• Miklowitz D, Biuckians A, Richards JA. Early-onset bipolar disorder: a family treatment perspective. *Dev Psychopathol* 2006;18(4):1247-65.

Drug Brand Names

Carbamazepine • various
Lamotrigine • Lamictal
Lithium • Eskalith, Lithobid
Methylphenidate • Ritalin
Olanzapine • Zyprexa
Quetiapine • Seroquel
Valproate • Depakene, Depakote

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that they were not coping well with stress. What starts leaking out as anxiety eventually may leak out as a full mood episode.

DR. KOWATCH: Are you seeing these 3 pathways in high-risk children of bipolar parents?

DR. CHANG: Yes, although sometimes the risk comes not from the parents but from a second-degree or more distant relative. We have seen plenty of families in which (as far as we can tell) the parents don't have any mood disorders, but a child has full bipolar disorder that began over time—as it usually does in bipolar offspring.

Children or adolescents who have first-break episodes after very little pre-morbid dysfunction comprise yet another subset. This group tends to present with episodic manic depression.

DR. KOWATCH: Do you think children with bipolar disorder have clear mood episodes?

DR. CHANG: Our research is trying to bypass that debate. We're trying to understand whether biomarkers in the brain or blood can be used to distinguish different types of bipolar disorders, rather than relying on symptomatology.

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Clinical Point

Many children who develop bipolar disorder had early anxiety, which may be a marker that they were not coping well with stress

Bottom Line

Children whose biological parents have bipolar disorder are at high genetic risk to develop the disorder. Pediatric bipolar disorder develops most often by 2 pathways: early-onset depression or early ADHD. A battery of genetic and brain imaging biomarkers may help improve early diagnosis. In the future, family psychotherapy and medications may be able to prevent 'kindling' of prodromal bipolar disorder.