

Special Article - Depression among Children and Adolescents

Children of Parents with Bipolar Disorder in the United States are at High Risk for Depression, Anxiety, and Multiple other Disorders: Implications for Research, Monitoring, Treatment, and Prevention

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***Corresponding author:** Robert M Post, Department of Psychiatry, George Washington University School of Medicine, Bipolar Collaborative Network, 5415 W. Cedar Lane, Suite 201-B, Bethesda, 20814, USA**Received:** November 12, 2015; **Accepted:** December 22, 2015; **Published:** December 23, 2015**Abstract**

In the United States (US) some two thirds of bipolar disorder in adults begins in childhood and adolescence compared to one third in Europeans. Two major risk factors for early onset include genetic/ familial loading and psychosocial adversity in childhood. There is a higher incidence of both of these factors in the US than in many other European countries. The parents, grandparents, and offspring of the US patients also have a higher incidence of illness than the Europeans, including more depression, bipolar disorder, alcohol and substance abuse, and "other" illness. Parents with mood disorders convey increased risk of mood and other childhood psychiatric disorders to their offspring via both genetic and epigenetic mechanisms. The incidence and earlier onset of these illnesses in childhood also appears to be increasing in the general population based on a cohort effect. Early onset bipolar disorder and depression have a more difficult course and prognosis than adult onset illness, in part related to a longer duration of the lag from illness onset to first treatment; yet this is a remedial risk factor. Increased vigilance for early onset mood and behavioral disorders based on the known clinical risk factors and more systematic monitoring of symptom emergence and response to treatment may help with earlier psychotherapeutic and pharmacotherapy interventions and help ameliorate the long term adverse consequences of childhood onset mood disorders. New research, clinical treatment, and public health initiatives are desperately needed.

Introduction

Two of the most powerful risk factors for childhood onset bipolar disorder and depression are a positive family history of these mood disorders and the occurrence of psychosocial adversity in childhood. To these well-known factors, we would suggest that being from the United States (as opposed to many European countries) is an additional risk factor interacting with the two above [1].

Multiple other risk factors are known, such that clinical history alone, without waiting for further genetic and neurobiological risk factors to be discovered and replicated, are already enough to encourage increased vigilance for childhood onset depressive, anxiety, and behavioral disorders. If, in addition to genetic and psychosocial risk factors, there is already the presence of prodromal symptoms, then careful monitoring is indicated, and psychosocial and pharmacological treatment should be considered as necessary [2,3]. In this brief commentary and overview, we highlight the need for greater awareness of childhood onset mood and behavior disorders with an emphasis that the incidence of both the vulnerability factors themselves and childhood onset bipolar disorder are greater in the US than many non-US countries. As such changes in the usual, typically delayed assessment and treatment paradigms in the US are warranted.

Vulnerability Factors for Childhood Onset Mood Disorders**Bipolar disorder or depression in parent**

Bipolar disorder in a parent conveys a very high risk of depression and anxiety in the offspring, as well as a wide range of other childhood psychiatric diagnoses. Axelson et al. [4] found that the following disorders occurred more often in offspring of a bipolar parent compared to offspring of community controls; this included an anxiety disorder (39.9% vs. 21.8%); depression (32.0% vs. 14.9%); ADHD 30.7% vs. 18.2%); disruptive behavioral disorder (27.4% vs. 15.3%); bipolar spectrum disorder 22.5% vs. 2.0%); and substance abuse 20.0% vs. 10.1%). Strikingly, 74% of the offspring of a bipolar parent had a major psychiatric diagnosis upon 6.7 years of follow up. Also startling was that in the matched community controls (parents without a diagnosis of bipolar disorder), about 50% of the offspring had a major childhood psychiatric diagnosis [4] indicating a very high prevalence of childhood onset disorders in the general population of the US. Similar findings of high risk for depression and many other psychiatric illnesses in the offspring of parents with serious psychiatric illness are seen in meta-analyses [5]. Axelson et al. [4] found that in offspring of a parent with bipolar disorder, the presence of depression, Bipolar-Not Otherwise Specified (BP-NOS),

or Disruptive Behavioral Disorder (DBD) predicted the conversion to full BP I or II disorder upon follow up, and suggested that early intervention in the treatment of these disorders could help prevent the conversion to bipolar disorder.

A family history of parental depression is also well-known risk factor for depression in the offspring. The long term follow up data of Weissman et al. [6] are particularly revealing. Upon 20 years of follow up, 82% of the offspring of a parent with unipolar depression had a major psychiatric diagnosis, with depression and an anxiety disorder being particularly prominent. If both parents are ill, the risks to the offspring are even greater [7,8]. Moreover, multi-generational influences are also apparent. Weissman et al. [9] found that a grandparental history of depression conveyed an additional risk for depression in the offspring, and the effect of grandparental illness alone was even greater than the effect of parental depression alone.

Other work has revealed that the degree of wellness of the parent with depression is important to the well being of the offspring.

Wickramanratne et al. [10] found that treating a mother's depression to full remission, as opposed to treating without achieving remission, resulted in less psychiatric illness in the offspring. A history of a suicide attempt in a parent is likewise a very high risk factor for a suicide attempt in the offspring [11].

US versus European illness vulnerability

In our Bipolar Collaborative Network we had 4 sites in the US (Los Angeles, Dallas, Cincinnati, and Bethesda) and 3 in the Netherlands (Utrecht) and Germany (Freiberg and Munich), here referred to as "Europe". The patients with bipolar disorder from the US were more ill than those from Europe. This included more: early onset illness, anxiety disorder comorbidity, substance abuse, rapid cycling, > 20 prior episodes, and more treatment refractoriness on prospective naturalistic follow up. Bellivier et al. [12] have replicated our observations of more childhood onset bipolar disorder in the US than in Europe, comparing data from the Pittsburg bipolar disorder case registry to that of 10 different European countries. Similarly, Etain et al. [13] found earlier onset bipolar disorder in the US than in France.

In our Network, the offspring of parents with bipolar disorder from the US had more depression, bipolar disorder, substance problems, and "other" illness compared to those from Europe [14] (post et al. 2015, JAD). This burden of illness was related to the overall burden of psychiatric illness in the offspring's parents (our Network patients) as well as the child's grandparents and great grandparents [15,16]. This illness burden in both grandparents and great-grandparents was greater in those from the US compared to Europe for depression, bipolar disorder, drug abuse, and "other" illness, indicating 4 generations of greater illness burden in those from the US compared to Europe (Table 1).

These data converge with those in high risk studies (because of a parent with bipolar disorder). Compared to those high risk studies conducted in Europe (or Canada), those conducted in the US appear to show a higher incidence of childhood onset bipolar disorder and many other illnesses (as reviewed in reference #1). Moreover, if one included a diagnosis of BP-NOS in the assessment, the 3 epidemiological studies that were conducted in the US also showed a

Table 1: Four Generations of those from the United States with more illness than those from the Netherlands and Germany.

	IV. Great grandparents	III. Grandparents	II. Patients with bipolar disorder	I. Offspring
Depression	***	***	N.A	***
Bipolar	***	***	N.A	***
Suicide atpmt	**	**	***	*
Alcohol	**	*	***	ns
Drug	*	*	**	*
"Other"	***	**	((**))	***

* = p<. 05; ** = p <.01; *** = p<.001 more of this illness in the US than in Europe
N.A.: not applicable; ns = not significant; (()) = an anxiety disorder comorbidity

much higher incidence of childhood onset bipolar disorder than the 3 conducted outside of the US [17] (Van Meter et al. 2011).

A cohort effect for depression and bipolar disorder

A variety of studies have shown the existence of a cohort effect (i.e., a younger age of onset and an increased incidence of illness in more recently born birth cohorts) for both depression and bipolar disorder [18-23]. Similarly there also appears to be a cohort effect for ADHD and substance abuse [20,24]. The basis of the cohort effects is not known, although multiple mechanisms have been postulated. Whatever the precise causes, it is apparent that the epidemic of childhood psychiatric disorders [25] is not only not self-correcting, but appears to be expanding in frequency and complexity.

Psychosocial adversity in childhood as a risk factor for bipolar disorder and depression

Childhood adversity, usually assessed by the presence of verbal, physical, or sexual abuse (or neglect) is a major risk factor for depression being later precipitated by stressors in adulthood [26,27]. Those with the common genetic variant of the short (as opposed to the long) allele of the serotonin transporter appear to be at particularly high risk. A variety of other gene-environmental interactions have also been preliminarily uncovered [28].

In our studies of the effect of childhood adversity on early onset and the adverse course of bipolar disorder, we found that verbal abuse alone (in the absence of the other forms of abuse) conveyed as much risk as the other forms [29]. We also saw that all three forms of childhood adversity were higher in the US than in Europe [2]. Thus, both greater genetic/familial vulnerability and psychosocial stress in childhood were related to an earlier onset and more difficult and complex course of bipolar disorder in our US versus European patients [1,15,16].

An Epigenetic Basis for the Long-Term Risks of Childhood Adversity

Data in animals and humans indicate that early environmental adverse events can change the structure of DNA, histones (around which the DNA is wrapped), and microRNA all three of which alter the ease or difficulty of transcribing messages from DNA. When acetyl or methyl groups are added to histones, they make DNA less or more tightly wound, and easier or more difficult to transcribe, respectively. Methylation of DNA usually results in inhibition of transcription.

These types of epigenetic changes can be highly persistent and

have now been shown to occur after childhood adversity in animals and humans in key components of the neurobiology of depression including the Glucocorticoid Receptor (GR) mediating adrenal cortical feedback [30-34], the GR chaperone FKBP5 [35], and the neuroprotective factor Brain Derived Neurotrophic Factor (BDNF) [36,37]. Adversity in children results in greatly increased evidence of epigenetic changes compared to depression alone or aging alone [38-41]. A striking new finding is that some epigenetic changes survive erasure in sperm and ova and can be passed on to the next generation even in the absence of contact with the offspring [42], although the extent that this happens in humans requires further study. Nonetheless, based on the available data transgenerational vulnerability to depression, stress, and substance abuse would appear to be mediated by 1) genetics, 2) epigenetic based on behavioral contact, and to a lesser extent 3) germ line epigenetic changes in the absence of behavioral contact.

The epigenetic basis of telomere length has not been fully studied, but both childhood adversity and the number of depressions experienced are associated with a higher percentage of shorter length telomeres which is not only associated with normal aging, but is a risk factor for multiple physical and disorders in adulthood [43-46]. Other risk factors of depression and bipolar disorder might include, poor diet, obesity and its attendant increase in inflammation [47] and each of these may also be more prevalent in the US than in Europe.

Clinical Implications

Whatever the precise genetic, epigenetic, and other environmental vulnerabilities mediating the high and likely increasing incidence of unipolar and bipolar disorder in the US, it is clear that new approaches to early recognition, treatment and prevention are indicated. Merikangas et al. [25] indicated that only about 20% of those with a bipolar spectrum diagnosis were in any kind of treatment. The incidence of depression and anxiety in youth are much higher than of bipolar disorder, but a proportional increase in treatment is not readily apparent.

The paradigm needs to change as emphasized by Shonkoff and Garner [48]. They stress that pediatricians need to be on the front line of inquiring about childhood adversity and its associated risks of medical and psychiatric maladies into adulthood. General practitioners and medical specialist physicians for adults likewise need to inquire about the health of their patients' children, and encourage monitoring and treatment as necessary.

Family Focused Therapy (FFT) and related psychotherapeutic approaches to depression, anxiety, and cyclothymia in children at risk for bipolar disorder because of a positive family history of bipolar disorder results in marked improvement compared to treatment as usual [49]. Other therapies have demonstrated positive effects [48]. Home visits [51,52], group interventions [53,54], and early childcare [55] have also proven to have long-term positive effects on behavior in various high-risk populations [51,52,55]. These and related interventions should be considered in addition to family-focused treatment in children at risk for bipolar disorder [56]. Similarly, therapy for children at high risk for depression has proven preventive for the onset of depression in preliminary studies [53,57].

While the pharmacotherapy approaches to ADHD in the US

are common, well known, and intensively studied by industry, the optimal approaches to anxiety, depressive, and bipolar disorders in very young children are vastly understudied, and the best approaches to the other externalizing syndromes such as Oppositional Defiant Disorder (ODD), Disruptive Behavioral Disorders (DBD), substance and alcohol abuse, and conduct disorder remain poorly delineated.

Clearly a new treatment research agenda is indicated for the vast array of childhood disorders, which not only are impairing, but are often the precursors to the adult forms of the disorder and their attendant risk of dysfunction, disability, and premature loss of years of life expectancy by way of suicide and cardiovascular disease. Such a needed paradigm shift in study, recognition, and treatment of these childhood disorders is not likely to instantly emerge, so other immediate steps should be taken in the meantime.

Parental education and awareness is a likely good place to start, particularly in those families where offspring are at high risk because of a parent diagnosed with depression or bipolar disorder. These parents are often acutely aware of the possible difficulties that emerge with these illness and their concerns should be met not with naive reassurance but with encouragement for watchful waiting, careful monitoring, or consultative evaluation depending on the course and severity of the child's symptoms. A focus on reducing risk factors with good diet, sleep hygiene, exercise, and mindfulness/meditation may begin to instill good habits early in life. Hudziak et al. [58] advocate that music, mindfulness, and exercise be universally available for all school children, and then greater intensity and other supports and therapies be provided for those who are already symptomatic.

A tool parents could use is available through the Child Network (informed consent and access to the Network is available at www.bipolarnews.org). The Child Network is for parents to rate children (age 2 to 12) with mood or behavioral disorders (or at risk for them because of a parental diagnosis of depression or bipolar disorder) on a weekly basis on a secure web site under a protocol approved by Johns Hopkins School of Medicine IRB. Parents briefly rate the severity of their child's depressive, anxious, ADHD, oppositional, and manic symptoms each Sunday night. They can then print out a longitudinal graphic of these symptoms for ease of visualization of illness evolution and response to treatment.

This graphic can then be brought to treating clinicians and physicians to help them better evaluate the severity and course of symptoms, need for psychosocial or pharmacological treatment, and response to any treatment utilized. Little is known about how the youngest children with mood and behavioral disorders are being treated in the community, and the Child Network will provide a first view of naturalistic treatment practices, their efficacy and tolerability.

We hope that clinicians will encourage their adult patients with mood disorder who have child that may or may not as yet have major mood or behavioral disorders to join the Child Network and begin to more carefully follow symptom development in a fashion similar to that of other medical illness. Careful monitoring of blood glucose in diabetes has greatly expanded patient wellbeing and longevity. Similar careful monitoring of blood pressure, cholesterol, and weight enhances management of cardiovascular disease, as is also the case for seizures in epilepsy, and inflammatory markers in juvenile rheumatoid arthritis.

The long term benefit of a specialty clinic that focuses on excellent psychosocial and pharmacological treatment, psycho-education, mood monitoring and patient engagement has been demonstrated by Kessing et al. [59] following a first hospitalization for mania. Two years of randomization to the specialty clinic versus Treatment As Usual (TAU) resulted in many fewer relapses. The differences continued and were further magnified over the next 4 years even though all patients had returned to TAU. Thus, early excellent care improves symptoms, illness management, and functioning, and changes the course of illness to a more benign form.

Conclusion

Early symptom monitoring in depression, anxiety, and many of the other common psychiatric illnesses of childhood may likewise help will illness recognition and appropriate intervention. Other approaches are also needed to begin to address what is too often woeful neglect of children with serious psychiatric illness, in part based on stigma, inadequate treatment resources, and a lack of systematic literature on optimal treatments, sequences, and combinations as well as preventive approaches [60] (Post and Kowatch, 2006; Post et al. 2013; [56]. Awareness of the extraordinarily high risks for multiple psychiatric illnesses in the offspring of a parent with bipolar disorder or depression, particularly in the US needs to be heightened. (JAD) A high family loading of psychiatric disorder, the presences of psychosocial adversity in childhood, and the emergence of prodromal symptoms are three major risk factors for the onset of more severe illness and should lead to careful evaluation and consideration of psychosocial and/or pharmacological treatment [56].

Childhood onset bipolar disorder and unipolar depression both run a more difficult course than adult onset illness, and this in part relates to the long lag between illness onset and first treatment which is longest in those with the earliest onsets [61,62]. The long lag before treatment is initiated is a modifiable risk factor that deserves attention and amelioration [3,63]. As in the Kessing et al. [59] study, early expert multimodal intervention may greatly improve the course of illness, and as such prevent many of the potentially devastating consequences of depression and bipolar illness including recurrences, increasing morbidity, cognitive dysfunction, treatment refractoriness [64] (Post et al. 2012), and premature mortality [65].

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