Bipolar Disorder in Children and Adolescents: from the Beginning to the Consequences

PERSPECTIVE

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Abstract

Bipolar disorder (BD) is a condition characterized by an alternation between phases of depression and mania. Its beginning is influenced by both genetic and environmental factors, causing neurological and psychological changes. In children, it is manifested through episodes of mood disturbance and pronounced psychosocial impairment, causing sleeping disorders and presenting a high rate of suicidal ideals. It has a very complex treatment, since you cannot neglect or exacerbate neither the episodes of mania or depression, taking them both in consideration when choosing the right medication and monitoring the symptoms and response to treatment. It is also a disease which has not a well defined process of etiology and pathophysiology. This study is a current literature review of a recurrent disease in psychiatry.

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Bipolar disorder (BD) is characterized by a cycling between depression and mania. Depressive symptoms are often more persistent and debilitating. [1, 2] BD affects up to 2.5% of the adult and adolescent populations [3-5], but its etiology and pathophysiology remain elusive [5]. Pediatric Bipolar Disorder (PBD) is a refractory and debilitating illness that affects 1% or 2% of the population [6, 7]. Youth with PBD are characterized by episodic mood disturbance (i.e. elevated mood and/or significant irritability) and pronounced psychosocial impairment, including poor self-esteem and coping, family stress, and dysfunctional family patterns [7-9]. Researchers remain divided as to whether instances of BD in children and adolescents represent a more potent presentation of the classic adult illness, a separate subtype of BD, a variant of other conditions such as attention deficit-hyperacti-

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vity disorder (ADHD), or a newly recognized illness unrelated to adult-onset BD [10, 11]. Researchers attempting to define the core features of child and adolescent BD have generally focused on bipolar I disorder (BD-I) [11-17].

It remains unclear the degree to which youths with episodic mania (bipolar disorder; BD) vs. those with chronic, severe irritability (severe mood dysregulation, SMD) should be placed in similar or distinct diagnostic groups [18]. Childhood-onset BD has been shown to be associated with shorter periods of euthymia, higher rates of psychosis, more recurrences, and greater likelihood of suicide attempts and violence than adult-onset BD [19]. Thus, the pathologic irritability in youths is impairing, common, and associated with adverse outcomes [20]. Clinicians and researchers have struggled to deter-

mine if severe, chronic irritability without episodic mania is a developmental phenotype of BD [18].

One criterion for validating psychiatric diagnoses is by diagnostic stability [21, 22]. Diagnostic stability may be defined as the degree where a diagnosis is confirmed at subsequent assessment points [22, 23]. Research has documented that PBD represents a discrete cluster of symptoms that can be validated by reliable assessment with stability over time [7, 24, 25] with temperamental characteristics and clinical manifestations that may differ from those with later adolescent-or adult-onset [7, 26].

Bipolar disorder has a neurodevelopmental component, the development of which involves genetic and environmental factors [27, 28]. It is also important to consider that BD is a progressive disease [5, 29], and that many structural alterations that

Figure 1: The Development of Pediatric Bipolar Disorder.

Figure 2: Aspects of Bipolar Disorder in childhood.

Figure 3: The Neurodevelopmental Theory and risk factors for the appearance of Bipolar Disorder.

have been associated to it may be mainly a scarring effect of repeated mood episodes [5, 30] and/or continued medication exposure [5, 31, 32]. BD has been thought to be related to schizophrenia (SZ) in certain respects, and as the neurodevelopmental hypothesis of SZ has become increasingly accepted, a similar hypothesis has been applied to BD [33-40]. Considering that brain development is a dynamic, genetically predetermined and environment-dependent process, cross-sectional imaging studies of the same disease in different stages of [e.g., childhood, late adolescence] may yield significantly different results. In this context, maternal smoking is associated with increased risk of attention-deficit/hyperactivity disorder (ADHD) [28, 41], conduct disorder [28, 42] and autism spectrum disorder (ASD) [28, 43] as well as psychiatric morbidity [28, 44].

It means that not only the clinical and methodological differences among studies should be taken into account, but also the ontogenetic aspects of the disorder itself [5]. Thus, one study showed it (maternal smoking) to be associated with an increased risk of mood disorders [28, 44], while two studies did not find any association with anxiety or major depression [28, 42, 45]. Several previous stu-

dies [28, 46, 47] have suggested that the association between maternal smoking during pregnancy and offspring behavioral problems and substance use is confounded by familial background factors [28]. Moreover, In children diagnosed with pediatric bipolar disorder, disturbances in the quality of sleep and wakefulness are prominent [48]. Sleep disturbances, such as insomnia, circadian rhythm alteration, and poor sleep quality with daytime sleepiness, are often reported by patients with BD and can be a hallmark of both manic and depressive episodes [49, 50]. These symptoms frequently persist when these patients are euthymic [49-51] and can contribute to baseline depressed cognitive and psychosocial function, which negatively impact treatment efficacy and quality of life [50, 52, 53]. A novel phenotype of PBD called Fear of Harm (FOH) associated with separation anxiety and aggressive obsessions is associated with sleep onset insomnia, parasomnias [nightmares, night-terrors, enuresis], REM sleep-related problems, and morning sleep inertia. Children with FOH often experience thermal discomfort (e.g. feeling hot, excessive sweating) in neutral ambient temperature conditions, as well as no discomfort during exposure to the extreme cold, and alternate noticeably between

Figure 4: Sleep and mood disturbances of Bipolar Disorder.

being excessively hot in the evening and cold in the morning [48]. An increased prevalence of Obstructive Sleep Apnea (OSA) among patients with psychiatric conditions has been reported, although most of the information is derived from adult population screening [50, 54, 55]. Sleep disturbance is a common feature of mood disorders. In children diagnosed with pediatric bipolar disorder, problems with the quality of both sleep and wakefulness are prominent, and include bedtime refusal, sleep onset insomnia, parasomnias, morning sleep inertia, and daily bouts of both hyperactivity and hypoactivity [48, 56, 57]. An associated observation is that children with BD alternate noticeably between being excessively hot in the evening and cold in the morning [48, 58, 59].

Besides this context, suicide in youth represents a significant public health concern, ranking as the third leading cause of death among children and adolescents in the United States [7, 60]. Further,

childhood-onset BD cases are more treatment resistant and have a worse prognosis than adult-onset BD [19, 61] which poses a great treatment challenge for clinicians and a heavy burden on affected families. Thus, there is a pressing need for greater neurobiological understanding of PBD [19]. The unique symptoms of PBD are associated with devastating consequences: PBD confers the highest risk for, and mortality from, suicide of all childhood disorders. Completed suicide rates for individuals with bipolar disorder are 15-times greater than the general population [7, 62], and early illness onset is associated with an increased risk of suicide attempts [7, 63]. Moreover, up to 50% of youth with bipolar disorder attempt suicide by age 18 [7, 64]. Thus, the early identification and intervention of suicidal behavior in this population is essential to alter the morbid illness trajectory [7].

By the way, childhood trauma can influence clinical outcome by inducing earlier disease onset, a

Figure 5: Risks between suicide and Bipolar Disorder.

greater number of episodes, a rapid cycling course and suicide attempts and increasing the need for hospitalization. Finally, specific types of childhood trauma are associated with different clinical features, [65, 66] like suicide attempts [66-68]. Numerous studies highlight the link between family environment and youth suicide attempts, with greater family conflict and lower family support differentiating youth attempters from nonattempters [7, 69, 70]. Such links may help explain the increased risk of suicide among youth with PBD, given the documented difficulties in parent stress, family communication and conflict that accompany this disorder [7, 71, 72]. Childhood trauma per se is only one of many possible pathogenetic factors [66, 73], but the according to the logistic regression analysis, emotional abuse is strongly linked to lifetime suicide attempts, apart of the type of BD diagnosed. This finding suggests the importance of adopting a dimensional approach towards suicidality in BD [66, 74]. This risk may be particularly acute given the documented dysfunction in the brain structures involved in coping skills (e.g., reduced activation in the dorsolateral

prefrontal cortex in concert with limbic overactivity) associated with PBD [7, 75-77], as well as the low self-esteem and hopelessness these youth report [7, 72]. Thus, BD is one the most devastating of all psychiatric disorders in terms of risk for suicide, need for hospitalization and suffering [2]. Therefore, the importance of assessing and addressing suicidality in children with PBD, and suggest that youth with lower self-esteem and greater family rigidity may be at high risk for future attempts. Interventions that address child cognitive and family risk factors via cognitive-behavioral and family-focused methods may reduce risk of suicidality in PBD [7].

In the neurological context, white matter abnormalities detected by Diffusion Tensor Magnetic Resonance Imaging (DT-MRI) have been consistently reported both in BD patients [5, 78, 79] and in their non-BD relatives in adulthood [5, 80-82]. Children and adolescents with BD also have been found to display decreased fractional anisotropy (FA), a measure of fibers coherence and organization, but findings differ across studies [5, 83-85]. Results on young, unaffected BD relatives are even more hete-

Figure 6: Neurostudies in Pediatric Bipolar Disorder.

rogeneous [5, 81, 86, 87]. It is important to notice that DT-MRI studies with unaffected BD relatives frequently include subjects with current or past history of other psychiatric diagnoses or subthreshold mood symptoms [5].

Moreover, Previous studies have shown reduced activation of right rostral ventrolateral prefrontal cortex together with increased activity in anterior cingulate, amygdala, and paralimbic cortex in PBD patients compared to healthy controls using a variety of cognitive tasks [19, 75, 76]. In pediatric BD, one study reported abnormal fronto-amygdala iFC in youths during a manic state [18, 88]. In each case, there is a growing body of evidence associating BD to gray and white matter abnormalities. Nevertheless, heterogeneity among studies is high and should be properly addressed.

One study offers another evidence for the hypothesis of neuroprogression in BD, suggesting that unmedicated pediatric patients do not carry observable white matter alterations, despite displaying the complete disease phenotype. Similarly, white matter abnormalities are also absent in healthy, young offspring of BD parents [5].

Further, the regions that showed significant amplitude of low frequency fluctuation (ALFF) change in the PBD mania group were parts of the basal ganglia and parietal cortex and the occipital cortex system, which are important for affect-processing, decision-making, and social cognition [19, 89, 90].

These findings support the hypothesis that the abnormality in resting-state activity of PBD mania patients is mainly located in the basal ganglia and parietal and occipital systems. Additionally, the ALFF approach may help with locating impaired regions in PBD patients in functional brain research, consistent with previous studies on other mental disorders [19, 91, 92]. Another study detected differences in iFC only at the basolateral amygdala which is implicated in threat conditioning [18, 93] and emotional encoding [18, 94].

In BD youths, amygdala volumetric abnormalities have been localized at the basolateral group [18, 95]. Future longitudinal studies are warranted to evaluate the progression of structural alterations in BD pediatric patients and to further investigate possible vulnerability markers in offspring at high-risk for BD [5].

About treatments, the one for adolescent or juvenile patients with bipolar disorder is modeled after some provided to adults. Therefore, successful long-term management of PBD requires a medication that treats both mania and depression, without neglecting or exacerbating one phase for the sake of managing the other [2]. For the majority of antipsychotic drugs, approved indications for youth in the United States are restricted to the treatment of schizophrenia and bipolar disorder [96]. According to the findings of several short-term pediatric trials for acute mania, one analysis suggests that second generation (atypical) antipsychotic (SGA) might also be more effective and better tolerated than traditional mood stabilizer (MS) on the maintenance stage of the treatment for PBD [2]. Thus, all bipolar spectrum disorders in children and adolescents are associated with high levels of clinical morbidity and distress, and that BD-NOS (bipolar disorder not otherwise specified) in particular may be an early and less differentiated phase of illness of BD-I or BD-II in children and adolescents and hence a target for early intervention, although longitudinal data are required to support this theory [11]. There is no traditional MS that possesses a similar degree of efficacy in treating both the manic and depressive phases of bipolar disorder. Most of these drugs are purely antimanic agents except for lamotrigine and lithium [2, 97]. However, lamotrigine is only approved by FDA for use on those over the age of 16 years. It is not commonly used in children because of the increased risk of fatal side effects, such as Stevens-Johnson syndrome in the young age group. Lithium, despite the indication for PBD, was used less often in recent years because of its narrow therapeutic windows and intensive monitoring requirement [2, 98].

This way, the phenomenology of bipolar disorder in children and adolescents remains a contentious topic in psychiatry practice and research. There is general acceptance that BD symptomatology often

has an onset in the mid to late teenage years [11, 99, 100] and that BD can be present in children and younger adolescents, but with a much less certain prognosis [10, 11, 101, 102]. This disorder is a life-long disease associated with frequent recurrences that requires long-term management using pharmaceuticals [2, 78].

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