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Pediatric Bipolar Disorder: Do we know how to detect it?

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Objective: To review the literature covering the epidemiology, clinical characteristics, longitudinal course, prognosis and clues for the assessment of the Pediatrics Bipolar Disorder (PBD).

Method: A computerized search in PubMed, looking for published articles since 1980.

Results: During the last years, the PBD diagnosis has proliferated largely, with some studies reporting incidences between 1% and 5%. In the past, some researchers reported that atypical symptoms could be more common than the classical symptoms in the PBD. However, current studies confirm the presence of typical mania symptoms in the youngest. Also, they confirm the utility of the diagnostic criteria DSM-IV in this population, with the PBD-NOS as the most prevalent phenotype. Those cases with irritability and without any other maniac symptom are still not clear, but the evidence shows a possible evolution towards others non-bipolar affective disorders. The PBD has high comorbidity, especially with ADHD and Disruptive Behavior Disorders. In the longitudinal evaluation, the PBD cases show high rates of relapse and persistent subsyndromical symptoms. The diagnosis is based in the clinical presentation, with collateral information provided by the family. Screening scales and standardized interview has been developed.

Conclusions: Now days is possible the diagnosis of PBD, although there is not enough information about the categorization and the longitudinal course of the PBD. Future studies are needed in order to clarify these shadows.

Keywords:
Bipolar disorder, children, adolescent, youth, epidemiology, incidence, prevalence, diagnosis, "prognosis, treatment.

Actas Esp Psiquiatr 2010;38(3):170-182

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El Trastorno Bipolar Pediátrico: ¿Sabemos detectarlo?

Objetivo: Revisar la literatura sobre el Trastorno Bipolar Pediátrico (TBP), centrándonos en su epidemiología, clínica característica, comorbilidad, curso y pronóstico y claves para su diagnóstico.

Método: Búsqueda sistematizada por PubMed de los artículos publicados desde 1980.

Resultados: En los últimos años se ha extendido el diagnóstico del TBP, señalándose una incidencia entre el 1% y el 5% según los estudios. Si bien se había señalado un presentación clínica atípica con un predominio de la irritabilidad y un curso crónico, estudios recientes observan síntomas patognonómicos de manía ya en edades precoces, demostrando la utilidad de los actuales criterios diagnósticos DSM-IV para el TBP, con un predominio del fenotipo BPNOS. Los casos donde la irritabilidad es el único síntoma, parece que evolucionarían hacia otros trastornos afectivos más que a Bipolares. En el TBP la comorbilidad sería muy elevada, especialmente con TDAH y los trastornos de conducta. En su evolución se observan elevadas tasas de recaídas y síntomas subsindrómicos persistentes. El diagnóstico debe basarse en la clínica, con información colateral de la familia. Se han desarrollado pruebas psicométricas con buena fiabilidad para el diagnóstico del TBP.

Conclusiones: En la actualidad es posible un diagnóstico fiable del TBP, pero persisten dudas sobre su categorización, y evolución en el tiempo. Son necesarios futuros estudios longitudinales que puedan aclarar su presentación.

Palabras clave:
Bipolar disorder, children, adolescent, youth, epidemiology, incidence, prevalence, diagnosis, "prognosis, treatment.

**.Dr. Méndez was at the University of Pittsburgh Medical Center (UPMC) for two years, with a grant from the Fellowship Program in Child and Adolescent Psychiatry, of the Fundación Alicia Koplowitz.*

INTRODUCTION

Bipolar Disorder (BD) has become one of the principal fields of study in modern psychiatry. Since the pioneer works of Angst and Perris in the 1960's, there has been a rebirth of the term bipolar[1], expanding its frontiers towards the concept of bipolar spectrum[2-4]. Thanks to the proliferation of research in this area, we currently know that in up to 60% of the cases, Bipolar Disease will begin in the infant or child stage[5,6]. We also know that an increase in affective disease is observed in comparison with the control groups in the families of bipolar patients, above all in those whose disease began before 18 years of age.[7-12] The evidence accumulated in this sense has shifted attention towards Infant-Child Psychiatry, reviving an old controversy: does pediatric bipolar disorder (PBD) exist?

Parallelly to this debate, we are observing an exponential increase in the number of visits with a diagnosis of PBD. Recently, Carmen Moreno et al.[13] studied the prevalence of bipolar diagnosis in outpatients in the USA during the period of 1994-95 to 2002-2003. The results obtained showed a global increase of the number of visits to psychiatrists in which BD was diagnosed. However, while the number of visits with a diagnoses of BD has increased twofold in the adult population, it has multiplied by 40 in the same period in the infant-child population (<18 years). Nonetheless, it should be mentioned that because the prevalence of BD in children is low, any increase is more noticeable. Blader et al.[14], analyzing the diagnoses on hospital discharge, also reported that the number of Bipolar diagnoses in those under 14 years of age had increased from 10% in 1944 to 34.11% in 2004 (OR/year= 0.25/year), with more modest increases in adolescents (14-18 years) (from 10.24% to 23.86%) and adults (> 18) (from 9.9% to 14.9%). Biederman et al.[15] studied the outpatient diagnoses in their clinic in Boston between 1991-2002, finding that 16% of the references would correspond to PBD. Due to the limited number of epidemiologic studies, we do not know if these results can be generalized to all the countries. It seems that this diagnosis would be less frequent outside of the USA, as concluded by Soutullo et al.[16], mentioning as examples the case of Spain, where only 4% of the outpatient diagnoses would correspond to PBD, the case of Brazil with 7.2% of outpatient diagnoses, or Finland with 1.2% of cases on the hospital level in Germany, Meyer et al.[17], using a questionnaire addressed to child psychiatrists, found PBD in 0.5% of the children and adolescents visited.

In an attempt to explain the differences between the USA and Europe, although there is no clear evidence, the possible iatrogenic effect of the stimulants and antidepressants, much more popular among the American child psychiatrists, has been pointed out[16,18,19]. Cultural differences or differences in educational styles and environmental factors would be other alternatives.[16] It is also possible that the PBD is not well recognized in other countries, as occurs with other disorders in childhood such as Attention Deficit Hyperactivity Disorder (ADHD) and Depressive Disorders (DD), it being possible to expect future increases in the prevalence of PBD. Furthermore, if we are speaking about a global increase in the number of bipolar diagnoses[20], we should search for other causal factors. A possible "new epidemic," has been ruled out since we cannot speak about a clear increase of the disease but rather of a proliferation of its diagnosis, so that there are two real possibilities: either beginning from a situation of infradiagnosis of Pediatric Bipolar Disorder[11], erroneously interpreting its clinical symptoms as other disorders (e.g ADHD), or the spreading of the concept of bipolarity is leading us to an overdiagnosis of a syndrome that is still not well defined[13,16,18].

Although we can currently conclude that the majority opinion in psychiatry is in favor of Pediatric Bipolar Disorder[21-27], it is true that we know little about this disease in its initial phases[28,29]. Are the same diagnostic criteria used in adults or do we need specific criteria in childhood?[30]. Can we speak about a continuum with the bipolar forms of the adult?[31-33], or speak about a phenotypically or genetically different subgroup?[34-37]. And even more important, will early intervention in these initial phases alter the prognosis?[38-40].

In this article, we will review the phenomenology and classification of Pediatric Bipolar Disorder, its course and prognosis, comorbidity and principal keys for the differential diagnosis. Our objective in this review is for it to serve as a guideline to facilitate early detection of PBD, providing the necessary instruments for its diagnosis.

METHODOLOGY

Using PubMed as a database, we reviewed the articles published in English from 1980 that included the terms "bipolar disorder," "children," "adolescent," "youth," "epidemiology," "incidence," "prevalence," "diagnosis," "prognosis," "treatment." We completed our review with a manual search in specialized journals and with cross bibliographic references.

EVOLUTION OF THE CONCEPT OF PEDIATRIC BIPOLAR DISORDER

We have stated that the debate on Pediatric Bipolar Disorder (PBD) is not new in Psychiatry. Since Aretaeus of Cappadocia first described choleric temperament in the first century, AD, mention has been made of its possible onset in puberty.[41] After Esquirol and the French alienists, in the 18th century, included this impression, describing the first cases of manic children.[20,41] Already in the 20th century, Kraepelin[42] observed an early onset (<10 years) in 0.4% of the cases in a sample of 900 manic-depressive patients and an onset

before 20 years in 40% of them, concluding that the disease could initiate in childhood, following a non-deteriorating chronic course in the adult life. Kraepelin's position was adapted by many of his peers, encouraging the first studies of mania in childhood.[43] However, beginning in the 1930s, this diagnosis was abandoned,[44] and the fact that the immaturity of the superego would make it difficult for affective diseases to develop at this stage was defended.[45] However, sporadic cases of mania in children continued to appear in the medical literature,[43] and then, 1960, Anthony and Scott clearly spoke about PBD with a review of a case having an onset at 8 years, establishing the key clinical symptoms in its diagnosis.[46]

Beginning in the 1970s, with the acceptance of Depressive Disorder in childhood (National Institute of Mental Health, NIMH 1972)[20,47], and the publication of the first treatment trials with lithium in children with behavior problems,[43] interest in PBD was renewed. At that time, the first attempts to classify it appeared, such as the diagnostic criteria of the neurologists Weingberg and Brumback,[48] or the primary symptoms of mania of Davis[49]. Finally, since the DSM III was published in 1980, the diagnoses of Bipolar Disorder in the child population has been possible.

PREVALENCE OF PEDIATRIC BIPOLAR DISORDER

The prevalence of Bipolar Disorder (BD) in adults would range from 0.4% to 1.6%,[50-53], although some authors have reported much higher prevalences, from 3% to 8%, if all of the bipolar spectrum is taken into account, finding elevated levels of social dysfunction, suicide attempts and family burden in all of the spectrum forms[54-57]. Although a mean age of onset at 20 years has been indicated,[58] a delay in the diagnosis of more than 10 years being usual[6,39], many retrospective studies performed by different groups around the world have shown that the symptoms had begun before 18 years of age in up to 60% of the cases.[5,6] Differences have not been found between genders in the global prevalence of BD, although the incidence in the extreme ages of life (<25 >76) could be greater in the male population.[59]

Up to date, few epidemiologic studies have been performed in the child population, and those published have important methodological differences, such as the use of different diagnostic questionnaires,[23,60] heterogeneity between the samples and biases due to the information source (parents versus children)[61]. One of the pioneer works in this field, the "Great Smoky Mountain Study of Youth"[62], did not find any manic episode in a general sample of 4500 children (9 -13 years) (North Carolina, USA), with a prevalence of Hypomania of 0.1% and the depressive episodes of 1.7%. However, both the age selected for this sample and the questionnaires used could have affected the negative results obtained. Lewinsohn et al.[63], also in a sample in the community, but this time focused on adolescents (1709 adolescents, 14-18 years) (Oregon, USA), found a BD prevalence of 0.9% (with a predominance of BPII and cyclothymia), pointing out that up to 5.5% of the total sample reported "subsyndromic symptoms of mania" (Periods of irritable, expansive or elevated mood, without fulfilling the DSM criteria for BD). Both groups compared with the case-control and the cases of Major Depression (MD) showed a higher level of dysfunction, with higher rates of psychiatric comorbidity (anxiety, behavioral disorders and substance abuse), suicide attempts and use of the mental services. A total of 893 subjects from the original sample were reevaluated at 24 years of age,[64] observing a progression of the subsyndromic group towards the depressive - anxious spectrum, but not towards the Bipolar disorder. A total of 1% of the depressive cases progressed to BD. In Europe, two studies in the general child population showed contradictory results: while in Great Britain, using a questionnaire that has still not been validated, no case of mania or hypomania was found in a sample of 10,438 young persons (5 - 15 years)[65], in Holland, in a sample of 2227 youths (13-18 years), they speak of a 0-0.9% and 0.9%-1.1% prevalence of mania and hypomania, respectively (this varying based on the informer, parents or child) compared to 1.3%-2.8% of the prevalence of Major Depression[66]. Another Dutch study, focused on children of bipolar patients (12-21 years), found a 3% prevalence of PBD.[67]

The real prevalence of Pediatric Bipolar Disorder could be greater than 1% of that shown by the studies. Akiskal[41] was one of the first to point out the possible masking of Bipolar Disorder as Major Depression in childhood, and it has been confirmed that between 20-30% of depressive children would evolve towards bipolarity in the adult age.[68,69] Other authors have stressed the frequent erroneous diagnoses of Bipolar Disorder in the initial phases.[47,70-72] Finally, it has been pointed out that the onset age could be much lower than expected. Therefore, Faedda et al.[71] found that more than 90% of their sample of Bipolar subjects would have begun before 13 years of age, with 75% of onset cases before 3 years. Axelson and Birmaher[32], within the COBY study of follow-up of 438 bipolar patients (between 7-17.11 years), also stress an average age of onset of 9.3 years. In the cases of early onset, there would be a predominance of males, although a progressive homogenization between genders with age is observed[15,71,73,74]. Similarly to Bipolar Disorder in adults, there is generally a delay in diagnosis of more than 7 years in the child population[22,71].

PEDIATRIC BIPOLAR DISORDER IN THE DAILY CLINICAL PRACTICE

According to that specified in the DSM-IV-TR[58], Bipolar Disorder is characterized by its episodic course, alternating between expansive or irritable mood states with depressi-

ve mood states or loss of capacity for pleasure (Table 1). However, it has been stated that the presentation of Pediatric Bipolar Disorder could be atypical.[20,26,27,30,45] The current diagnostic criteria are only fulfilled in 50% of the cases,[26,71] either because the time criteria are not adequate,[32,75] or due to the predominance of other cardinal symptoms (irritability versus euphoria, hyperactivity, mixed affective states) or due to its insidious and chronic course[15,26,33,34].

Clinical symptoms characterized by Pediatric Bipolar Disorder

The clinical phenotypes in the infant-child population must be clarified in order to be able to advance both in the diagnosis and treatment, as well as in the etiopathogeny and genetics, of Pediatric Bipolar Disorder.[76-78] Several classification proposals have been suggested for this.

Some authors suggest using onset age as a differentiating element, distinguishing 2 phenotypes of Pediatric Bipolar Disorder:[34,73,79] *PB Childhood onset" or "very early onset"* (<13 years), and PB *Adolescent onset" or "PB early onset")* (≥13-<18 years) (Table 2). The child onset forms would be characterized by the predominance of the male gender[15,79], an insidious onset[26,73], more irritability and mixed pictures[26,34], rapid cycling[34], chronic course[34,79,80] an elevated rates of comorbidity[15,35,73,79]. These could be a specific subtype of Bipolar Disorder[25,37] with greater family aggregation, both for Bipolar Disorder[81] and for ADHD[82,83] or for a wide margin of psychopathology in the family[7], specific treatment needs and worse prognosis in the adult life, with greater comorbidity with substance abuse, low syndromic remission and elevated treatment resistance.[22,34,84,85] Onset forms in adolescents age would be more similar to the adult bipolar ones[38], there being no differences between genders.[15] They would have an abrupt onset in form of complete depression of our manic episode,[73] greater prevalence of psychotic symptoms,[73,86] especially in form of delusion of grandeur,[85] episodic course, and lower cycling, with lower comorbidity rates than in the children[79,87].

However, clinical differences were not observed in all of the studies between the child versus adolescent presentation.[15,23,33,35,87,88] In line with these results, a new form of classification of Bipolar Disorder has recently arisen according to onset age: a subgroup of early onset, which would group all the infant-child forms (<18 years); a subgroup of intermediate onset (27 years); and a subgroup of late onset (>46 years)[89,90]. The forms of early onset would have a greater genetic component,[36,90] versus a multfactorial model in the late forms.[90]

Another possible alternative of PBD classifications would be to use a dimensional approach, an especially profitable strategy in genetic studies.[76,91] On the contrary, there are many authors who defend the validity of the current classification systems[24,31,32,78,88], adapting them to the infant-child population.

In order to reach a consensus on the lines of research in the diagnosis of PBD, the National Institute of Mental Health (NIMH, USA)[30] organized a round table of experts in August 2001. At the end of the meeting, there was an unanimous agreement about the possibility of diagnosing Pediatric Bipolar Disorder with the current DSM criteria, using fours years as the cut off. Furthermore, two phenotypes within pediatric BP were established: narrow-phenotype PBD and broad-phenotype PBD. The narrow phenotype would include Bipolar Type I and Type II phenotypes. The broad one would group a heterogeneous group of youths who either complied with the time criteria or did not or who did not have the cardinal symptoms. It would be an experimental diagnosis, that would provisionally be called bipolar disorder not otherwise specified (BPNOS) phenotype (Table 3).

Long-term follow-up studies of PBD have confirmed the validity of the narrow phenotype. One of the pioneer works in this field, "Phenomenology and Course of Pediatric Bipolar Disorders"[35,92,93], followed up 268 youths (7-16 years) for 6 years, with diagnoses of BD-I (93) and ADHD (81), and healthy controls[94]. The results obtained seem to confirm the presence of specific symptoms in the BP-I phenotype. In addition to elevated mood and grandiosity, that are necessary as inclusion criteria, the BP-I would characteristically and differentially occur with the ADHD: flight of ideas/racing thoughts, decreased need to sleep and hypersexuality[24,35]. Irritability, verbosity, distractibility and increased energy, although significantly more frequent in BP-I, would also be present in the ADHD[24,94]. In 60% of the BP-I, there would be psychotic symptoms, mixed states between 50% and 80%, and ideation/suicide attempts in 20%, making up a clinical picture having elevated severity (Table 3)[35,95,96]. Eighty-six of the 93 BP-I were evaluated at 6 months, 2 years and 4 years of follow-up, confirming stability in the time of pediatric phenotype BP-I[24], with its chronic course, elevated rates of relapses and interepisodic subsyndromic symptoms standing out[95]. Finally, comparing the family backgrounds in the 3 groups, a greater familial aggregation for PB would be observed, with an early phenomenon regarding their parents[92]. As a whole, the results obtained show a continuity between pediatric BP-I and the BP-I adult forms[95]. In the pediatric BP-I, the characteristic symptoms of mania would be present, with a chronic and severe course, also found in 20% of the cases of adult BP[97].

The validity of the narrow phenotype, including for the first time within this group all of the DSM-IV forms (BP-I, BP-II and BPNOS) with modified criteria for the infant-child population (see table 3), was also confirmed in the project

Table 1 Diagnostic criteria: Adapted to the "Manual Diagnóstico y Estadístico de los Trastornos Mentales. DSM-IV-TR", Masson 2003 (58)[58]

	BIPOLAR DISORDER I	BIPOLAR DISORDER II
Definittion	Clinical course characterized by one or more manic episodes or mixed episodes. It is common for the subjects to also have one or more major depressive episodes	Clinical course characterized by the appearance of one or more major depressive disorders accompanied by at least one hypomanic episode
Basic Symptoms	- Manic episode: a differentiated period of expansive mood + ≥3 or irritable mood + ≥4 : . Exaggerated self-esteem /grandiosity . Decreased need for sleep . More talkative than usual / logorrhea . Flight of ideas or racing thoughts . Distractibility . Increase of intentional activity (social, laboral, sexual) or psychomotor agitation . Excessive involvement in pleasant activities - The symptoms generate a significant deterioration, or hospitalization has been necessary, or there are psychotic symptoms present	- Manic episode: differentiated period of expansive or irritable mood together with symptoms characteristic of mania - The episode is not sufficiently severe to provoke a significant work or social deterioration. Hospitalization is not necessary. No psychotic symptoms are observed
Duration	≥ 1 week	≥ 4 days

Table 2 Phenotypes of Pediatric Bipolar disorder based on onset age

	BIPOLAR DISORDER OF THE CHILD	BIPOLAR DISORDER OF THE ADOLESCENT
Demographic characteristics	Onset at <13 years Predominance of males Family backgrounds of BP, ADHD, others	Onset between ≥13-<18 years Women=men
Basic Symptoms	Irritability, mixed affective states, Rapid cycling Elevated comorbidity	Complete depressive/manic/mixed episodes Greater prevalence of psychotic symptoms
Evolution	More chronic course Treatment resistant Poor prognosis	Episodic course Classical BP phenotype of the adult

"Course and Outcome of Bipolar Youth" (COBY)[31,32], a multicenter, prospective study of more than 400 bipolar patients (7-17.11 years). BP-I would be the most frequent clinical presentation in these ages (58.2% of cases), followed by the BPNOS (34.9%), with a very low incidence of the BP-II phenotype (6.8%)[32]. The BP-I and BPNOS cases would be slightly younger than the BP-II, with a prepuberal onset in most of the BPNOS, and a homogeneous distribution between both genders. The BP-II would have a post-pubertal onset, with a possible predominance of the female gender[31]. The first results at 2 years of follow-up confirmed the stability of the BP-I. However, the BPNOS and BP-II forms would be more unstable in this population, it having been observed that up to one third of the BPNOS cases would evolve to BP-I or BP-II (20% and 10%, respectively), and 21% of the BP-II to BP-I[31]. When the clinical symptoms characteristic of each phenotype are compared, an elevated similarity between the PB-1 and BPNOS is observed[32]. Both phenotypes would share the fundamental phenomenological symptoms of mania, principally elevated or expansive mood, irritability, grandiosity, verbosity, flight of ideas/ tachypsychia and distractibility. Both phenotypes would have the same comorbidity, especially with ADHD and BD, and the same family background. BP-I and BPNOS would basically be differentiated by the time criterion and the grade of clinical severity. The BPNOS last less time than that required by the DSM-IV for the diagnosis of BP-I and II, and the symptoms are less severe. The BP-I cases would have a higher rate of psychoses (35% compared to 17.6%), more previous hospitalizations (66% vs 29%), and a greater number of psychotropic treatments[32]. The BP-II cases would begin late, presenting a less severe clinical picture, with psychosis during the depressive episodes in 20% of the cases and a lower number of hospitalizations. They would have more family backgrounds of suicide and

Table 3 Phenotypes of Pediatric Bipolar Disorder with categorial criteria

	NARROW BP PHENOTYPE			BROAD BP PHENOTYPE	
	BPI (1,2,3)	**BPII (1)**	**BPNOS (COBY) (1)**	**INTERMEDIATE PHENOTYPE (4)**	**SEVERE EMOTIONAL DEREGULATION (SED) (3,4)**
Subtypes and diagnostic criteria	**DSM-IV (1,3)**: Period differentiated by expansive or irritable mood + ≥3 or ≥4 symptoms B. Duration > 7 day **Modified DSM (2)**: Period differentiated by expansive + ≥3 symptoms B Duration > 2 weeks Significant deterioration, hospitalization or psychotic symptoms	**DSM-IV (2):** Period differentiated by expansive or irritable mood + ≥3 or ≥4 symptoms B Duration >4 Days There is no deterioration, no hospitalization, no psychotic symptoms	(1) Period differentiated by expansive or irritable mood +: - ≥2 (≥3 if irritable) symptoms B - Significant functional deterioration - Duration of episode: ≥4 hours/day - Symptoms present ≥4 days, not necessarily consecutive (e.g. 2 days with 2 episodes/day; 4 days with 1 episode/day)	(4) **(Hypo) mania -NOS** (Hypo) mania of 1-3 days **(Hypo) mania- irritable** Children who fulfill the (Hypo) mania criteria of the DSM, with irritability as symptom instead of elevated mood	(4) Ages 7-17 year, onset symptoms <12 y - Sadness or range - Hyperarousal (>3): insomnia, agitation, distractibility, flight of ideas, pressured speech, intruisiveness - Symptoms present for at least 12 months. Symptom-free period <12 months - Significant functional deterioration
Basic Manic Symptoms	*Present >70% cases (1,2,3)* - Elevated or expansive mood - Irritability or anger - Grandiosity - Verbosity - Flight of ideas / Racing thoughts - Verbosity - Distractibility - Decreased need for sleep (1,3) - Increase in intentional motor activity / psychomotor agitation (3) *Presents <70% cases (1,2)* - Decrease need for sleep (40%) (2) - Increase of intentional activity (60%) (1): Hypersexuality (45%) (1,2)		*Presents >70% cases (1)* - Elevated or expansive mood - Irritability or anger - Grandiosity - Verbosity - Flight of ideas / Racing thoughts - Distractibility Symptoms present, but with less intensity than in BPI (1) *Presents <70% cases (1)* - **Decreased need for sleep (56%)** - **Increase of intentional activity: Hypersexuality (24%)**		*Presents >70% cases (3)* - Irritability - Psychomotor agitation
Other symptoms	- Psychosis: 35% (1)-60% (2,3) - Suicidal Ideation: 77% (1); suicide attempts: 35% (1)-45% (3) - Previous hospitalizations: 66% (1) - Comorbidity: ADHD 60%-(1)-77% (3)-86% (2), ODD 41% (1)-61% (3)-78% (2), AD 13% (1,2)-22% (3), AD 37% (1)	- Psychosis: 20 % (1) - Suicidal Ideation: 93% (1); suicide attempts: 43% (1) - **Previous hospitalizations:** 53% (1) Comorbidity: ADHD 43%, TND 23%, AD 13%, **AD 60%** (1)	- **Psychosis: 17'6%** (1) - Suicidal Ideation: 72% (1); **suicide attempts: 21% (1)** - **Previous hospitalizations: 29%** - Comorbidity: ADHD 62%, ODD 40%, AD 12% , AD 38% (1)		- **Psychosis: 38%** (3) - **Suicide attempts: 25%** (3) - Comorbidity: ADHD 67%, ODD 81%, AD 33% (3)

Table 3 (continuation)

Course	Stable (1) (2)	BPII ¿? BPI ¿? (1)	BPI ¿? (1)	TDAH ¿? TA, DM¿? BPI with poor diagnosis¿? (4)

(1) Birmaher & Axelson, 2006 Hiperactividad; (2) Geller, 2004 Desafiante; (3) Bhangoo, 2003; (4) Leibenluft, 2003
Note: the results in bold show significant differences regarding the BP1 group
ADHD: Attention Deficit Hyperactivity Disorder; ODD: Oppositional Defiant Disorder; AD: Antisocial behavior disorder; AD: Anxiety Disorder; MD: Major Depression; BP: Bipolar Disorder

greater comorbidity with the Anxiety Disorder (AD)[32] (Table 3). In the three phenotypes, a chronic course would be observed, with symptoms in more than 60% of the evolution time. In the BP-I and BP-II, clear syndromic episodes with elevated recurrence rates would be distinguished, compared to the BPNOS in which the subsyndromic symptoms would be observed persistently[31].

Recently, Masi et al. replicated the COBY study in a sample of 217 PB (8-18 years) (98), also observing a predominance of the BPNOS phenotypes in the younger groups with prepuberal onset, with a chronic course, versus a more episodic course in the BP-I and BP-II.

Although the results obtained up to date seem to confirm the validity of BPNOS in the PBD, and its inclusion in the narrow phenotype, it still cannot be foreseen what its evolution will be in the adult life. In some cases, the atypical symptoms will only be the form of initial presentation of Bipolar Disorder in children, evolving towards BP-I and BP-II with age[31,32]. Other cases, such as BPNOS, will persist in the adult life. Finally, in a reduced group, the maniform symptoms may be only the prodromal phase of another condition.

The validity of the broad phenotype continues to be a controversial subject. Leibenluft and Dickstein[78,99] have proposed limiting it to the cases of Severe Emotional Deregulation (SED), young people with negative emotional regulation, in the form of severe anger attacks, on a chronic hyperarousal condition (hyperactivity, distractibility, etc.). Thus, they distinguish two clinical presentations between the "possible" cases with PBD[78,99]: one group of young people with chronic irritability, Severe Emotional Deregulation (SED), that form the broad phenotype; and a group with euphoria or episodic irritability that would include 2 subtypes, the narrow phenotype if the time criteria of DSM-IV (>7 days, <4 days) is fulfilled, or the intermediate phenotype if they are not fulfilled (table 3). It must be indicated that almost all the subjects included by these authors as SED have behavioral/oppositional disorders and/or, ADHD. In the only study published up to date comparing the characteristic symptoms between the cases of pediatric bipolar disorder (PBD) with episodic presentation (narrow phenotype: BP-I), and the cases with chronic presentation (broad phenotype: SED), they only found 2 symptoms of mania in the SED group, that is, irritability and psychomotor agitation compared to the presence of all the cardinal symptoms of mania in the BP-I; BP-I and SED group and they also would be differentiated in the grade of severity, with greater rates of psychoses and suicide in the BP-I group[75]. Both groups have deficiencies in emotional regulation compared with the healthy controls, but they could be different in the reward circuits and cognitive flexibility[99,100]. In the long-term follow-up of these patients, it seems that subjects with chronic irritability (SED) evolve more towards Major Depression (MD), Anxiety or ADHD than towards mania[101,102]. Lewinsohn[64] also observed a similar evolution in his sample of patients with bipolar "subsyndromic symptoms." Up to now, no follow-up data on the intermediate phenotype has been published.

Comorbidity and differential diagnosis of Pediatric Bipolar Disorder

Within the PBD, the ADHD would be the most frequent comorbid disorder, with a prevalence between 11 and 90%[31,33,71,74,75,95], superior in the very early onset forms (<12 years) and in males[15,35,71,73,79,83,96]. Behavior Disorders (BD) would occupy the second-place infrequency, and could be related to a worse functioning level, with worse scholastic performance, greater backgrounds of admissions and more previous treatments[37,103]. Oppositional Defiant Disorder would be the principal diagnoses, present in 9-90% of the cases, with a lower percentage for Antisocial Disorder, of 6% to 34%[26,31,33,71,74,75,87,95,98,103]. It is not clear if there are differences between childhood or adolescent onset or between genders[15,33,71,79,87,96]. Comorbidity with anxiety would occupy the third place, with general rates of 17% to 60%[26,31,33,71,74,95]. Within this group, the most frequent disorders would be Generalized Anxiety Disorder (6-50%), Separation Anxiety (5-56%) and Obsessive-Compulsive Disorder (7-47%)[15,26,79,87,95]. Up to 40% of the cases would have

Table 4 Mimicking Disease and Drugs. Adapted b Lewis, 2004[106]

Diseases and drugs that may mimic manic symptoms in Children and Adolescents
Diseases that may mimic manic symptoms:
Infectious: Encephalitis, Influenza, Syphilis, HIV
Endocrine: Hyperthyroidism
Neurological: Temporal lobe infarction, Brain injury, Multiple sclerosis, Infarction, Wilson Disease
Systemic lupus erythematosus
Tumors: Thalamic, Gliomas, Meningiomas
Others: substance abuse, anemia, hemodialysis
Mood Cycling Increases:
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Serotonin–norepinephrine reuptake inhibitors
Aminophylline
Corticosteroids
Sympathomimetic amine (e.g. pseudoephedrine)
Antibiotics (e.g. clarithromycin, erythromicin, amoxicillin)

Agoraphobia, and 20% Panic Disorder (PD (7-29%) and other phobias[15,26,87]. There would be no differences between children and adolescents, except for separation anxiety disorder being greater in children compared to adolescents[15]. In every case, the female gender would predominate[74], as well as phenotype BP-II compared to the BP-I/BPNOS[31,98]. It seems that the comorbidity between Panic Disorder and PBD would be associated to greater prevalence of psychotic symptoms and greater suicide risk[104]. Substance Abuse Disorders would be uncommon, 4-18%[31,33,71,74], and would mainly occur in adolescents[15,33].

In the differential diagnosis of PBD, its elevated overlapping with ADHD and the BDs should be taken into account. Cases of atypical ADHD with late onset (e.g. in those over 15 years) and sudden onset or ADHD and BD with fluctuations in time based on mood, and low response to treatment or the presence of symptoms characteristics of mania[94] together with hallucinations or psychosis and affective familial background, should always suggest the possibility of a PBD[105]. PBD may also be confused with Schizophrenia if the psychotic symptoms are prominent. An abrupt onset, without affective flattening or abulia, and affective familial backgrounds, would be more characteristics of PBD.[105,106] We should also consider the possibility of PBD in the cases of early onset Major Depression, with psychotic symptoms, elevated psychomotor inhibition and treatment resistant.[107] Another confounding source would be Generalized Development Disorders, in which periods of irritability, mood changes and severe tantrums are frequent if the patient's routine is altered.[108]. Finally, we should rule out other medical or drug diseases that could mimic manic symptoms (table 4).

Clinical course and prognostic factors of Pediatric Bipolar Disorder

It has been indicated in Pediatric Bipolar Disorder (PBD) that the earlier the onset age, the worse the prognosis,[5] and this seems to be confirmed by the longitudinal studies of pediatric bipolar patients. In the study of Geller et al.[95], in the COBY study[31], and in a recent analysis of 71 PBD-BP-I of DelBello et al.[109], syndromic recovery not exceeding (from 87% to 68% according to the sample) was observed[31,95,109], with symptomatic and functional recovery of 39% at one year of follow-up[109]. PBD would be characterized by a morbid course, with frequent syndromic recurrences, in 52-70% of the cases and persistent symptoms in more than 60% of the evolution time[31,109]. PBD-BPI and BPII, compared with BPNOS, would follow a more episodic course, with more recurrences, of manic and mixed predominance in the BP-I[31,95,109], and depressive in the BP-II[31]. On the contrary, the BPNOS would have a longer course, with persistent symptoms having manic or mixed predominance, but of less intensity. They would take longer to recover, but once that occurs, they would remain asymptomatic until recurrence[31]. In all the cases, elevated rates of cycling, mixed episodes and frequent fluctuations in the symptoms intensity over time would be observed[31,95] PBD-II and NOS would also have high rates of conversion in their evolution[31]. Factors indicating poor prognosis are the presence of psychotic symptoms[31,95], a longer duration of the child-onset disease, and the BPNOS forms[31]. Low socioeconomic level[31,109] and lack of maternal affection[95] would also have a negative effect.

PBD appears at a significant moment in the development and growth of the child, limiting his/her learning and social interaction capacities. The earlier the appearance of the disorder, the more it will affect the child's normal development. We also know that BD increases the risk of suicide, homicide, substance abuse, psychosis and work, academic and social problems at any age, and risk of pregnancy and sexually contagious diseases and slowly progresses after puberty.[60,63,110]. Only early intervention at these ages could decrease the elevated morbidity associated to this disease.[21]

Pediatric Bipolar Disorder: How can we diagnosis it?

The American Academy of Child and Adolescent Psychiatry recommends the active search for manic symptoms in all of the first psychiatric interviews[111], with specific questions on spontaneous periods of mood changes accompanied by psychomotor activation, previous depressive episodes and backgrounds of affective disorders in the family. If after the first visit, symptoms consistent with mania are suspected, it is recommendable to have a clinician experienced in affective disorders of the child and adolescent carry out an extensive evaluation, interviewing both the child and at least one

of his/her parents[107,112]. The diagnosis should always be made from a longitudinal perspective, considering both the evolution of the symptoms and the context in which they occur and their functional repercussion. The symptoms should exceed the expected reaction for a child of the same age in the same circumstances. It is important to establish a good time sequence, defining the onset form, remission and worsening periods, response to previous treatments, stress factors and precipitating factors of each episode. It may be useful to recur to significant dates such as birthdays, vacations, school semesters or courses to help the patient and family remember. Within the current episode, the worst and best moments, and the current level of functioning should be clarified with the patients and the main problems to be treated in order of importance should be established. In each interview, suicidal ideation (and homicidal ideas), should be studied given the high risk in this population.[110,113] The history should be completed with specific questions on the child's development and medical background and previous treatment in order to rule out organicity (Table 4). Family backgrounds, with the treatments received and level of response, should be reviewed. Finally, in order to reach a definitive diagnosis and evaluate the need for treatment, the clinical severity of the episode must be established, the FIND system[112] being useful to help the clinician in his/her decision:

- Frequency: the symptoms occur most of the days in the week
- Intensity: the symptoms are sufficiently severe to cause extreme distortion in a functioning area or a moderate one in two or more areas
- Number: the symptoms occur three or four times a day
- Duration: the symptoms occur 4 or more hours a day in all, not necessarily contiguous.

For the moment, there are no determining biological or neuroimaging tests. The final diagnosis will be based on the symptoms, with the recommendation to follow the DSM-IV criteria as a guide (Table 1)[30,111]. Several hours are needed to be able to make a good diagnostic interview or to space the information collection into several visits. In the research programs, semistructured interviews are generally used for the diagnosis of PBD, such as the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL)[114] or a modified version, the Washington University in St. Louis K-SADS (WASH-U-KSADS)[115], that are presently not essential, and that are too long to apply in a standard outpatient clinic. A valid alternative is to fill out the information with specific questionnaires aimed at the parents, who can fill them out in the waiting room, such as the Parent General Behavior Inventory (P-GBI)[116], or its short versions, the P-GBI-10[117], the Child Bipolar Questionnaire (CBQ)[118], or the Mania Rating Scale for Parents (CMRS-P)[119]. There are versions in Spanish for all of them. However, it must be mentioned that these questionnaires are for general conditions, and not diagnostic questionnaires. More validation studies are needed to confirm their validity to differentiate between PBD and other psychiatric disorders. Different questionnaires aimed at minors and their professors have also been developed. However, lower reliability than those questionnaires of the parents has been observed.[117,120]

The clinician may also use symptoms scales to establish the severity of the episode and monitor response to treatment. Some examples would be the KSADS Mania Rating Scale (KMRS) derived from the KSADS[32], or the Children Depression Rating Scale (CDRS)[123]. The Young Mania Rating Scale (YMRS)[121,122] can also be used, although it was developed for the observation of adults hospitalized for mania and not specifically for children. The YMRS and the MDQ have self-registry forms for the parents, the P-YMRS[124] and the P-MDQ[117], with good reliability[117,125]. It is also recommended that the parents fill out a diary of symptoms with colors or scales form 1 to 10 for the daily mood changes, which could be reviewed at each visit.[105]

Once the patient has been stabilized, other comorbidities or deficits that should be examined with the specific instruments may be highlighted.

Finally, it should be indicated that although the presence of manic cases in very early ages is possible, diagnosis in those under 6 years is debatable[111]. The interview must be adapted to the development level of the child and it should be filled out as far as possible with the direct observation of the child in his/her home.[30]

CONCLUSIONS

In recent years, doubts regarding the diagnosis of Pediatric Bipolar Disorder (PBD) have been clearing up. It seems that the prevalence of the PBD would be 1%, although more studies are needed to confirm it. Considering the cognitive and emotional development of the child, the PBD would have a similar clinical presentation to that of BD in adults. The pathognonomic symptoms of mania would already be observed in the very early ages of life, frequently alternating with depressive episodes and mixed states. The utility of the current DSM-IV criteria for the diagnosis of PBD would also be confirmed, with a predominance of the BPNOS phenotype, given the limitation of the time criterion. However, on the contrary to the adult forms, the PBD would have a greater family burden and more mixed presentations, fluctuations in the affective state, and except for substance abuse, more comorbidity with other psychiatric disorders such as ADHD and BD. The rapid fluctuation of affect accompanied by the presence of elevated comorbidity with other disorders and the difficulty of the children to recognize and express their emotions as well as the specific characteristics of the different stages of neurodevelopment, may complicate the

adequate diagnosis of PBD and explain the difficulties in the treatment of these children. The clinician may use different more or less specific instruments, filling out the information with the parents or caregivers.

Given the extensive literature on PBD, we have focused our review on defining its phenomenology and diagnosis. Future revisions that complement the treatment and the early intervention strategies are necessary.

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