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Research report

Two-year follow-up of treated adolescents with early-onset bipolar disorder: Changes in neurocognition

Sara Lera-Miguel [a,*], Susana Andrés-Perpiñá [a,b,d], Mar Fatjó-Vilas [b,c,e], Lourdes Fañanás [b,c,e], Luisa Lázaro [a,b,d,f]

[a] Department of Child and Adolescent Psychiatry and Psychology, Institute of Neurosciences, Hospital Clínic, Barcelona, Spain
[b] CIBERSAM, Spain
[c] Institut de Biomedicina, Universitat de Barcelona, IBUB, Spain
[d] Institut d'Investigació en Biomedicina August Pi i Sunyer, IDIBAPS, Spain
[e] Department of Animal Biology, Universitat de Barcelona, Spain
[f] Department of Psychiatry and Clinical Psychobiology, Universitat de Barcelona, Spain

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ABSTRACT

Background: Few studies have analyzed the course of neurocognition in treated children and adolescents with early-onset bipolar disorder (EOBD) and shown improvements in attention, working memory, and verbal memory after treatment. The aim of this study was to determine the progress over two years in neuropsychological performance of a sample of medicated adolescents with EOBD compared to healthy controls (HC).

Methods: Twenty adolescents, diagnosed in clinical setting as DSM-IV bipolar disorder, treated for two years, euthymic, and 20 gender and age-matched HC were assessed at two moments in reasoning, verbal and visual memory, working memory, speed, visual-motor skills and executive function. Multivariate analyses of variance was carried out to analyze the differences between groups over time, and to monitor the influence of psychotic symptoms and type of mood-stabilizer.

Results: The entire sample improved on verbal and visual memory tests (verbal recall $p < 0.01$; visual recall $p < 0.001$). Moreover, patients improved more than controls in verbal reasoning ($p < 0.01$), working memory ($p < 0.01$), processing speed ($p < 0.01$) and visual-motor skills ($p < 0.001$). Psychotic symptoms and treatment with lithium were associated with poorer development in executive control tasks.

Limitations: Sample size was small and groups were re-evaluated in slight different follow-up periods. Doses of antipsychotics drugs over time were not controlled.

Conclusions: Processing speed and visual-motor skills in the EOBD group normalized during follow-up. Executive functioning, working memory, and verbal and visual memory remained impaired in patients versus controls. The knowledge of cognitive deficits due to normal course of illness or to drug effects allows better therapeutic strategies.

1. Introduction

Early-onset bipolar disorder (EOBD) defines the first appearance of this disorder in adolescence or childhood. It affects up to 2% of this age group and its premature course has been associated with a worse life outcome and higher rates of comorbidity (Carlson et al., 2009; Lazaro et al., 2007). A very early onset of the disorder, i.e., before 13 years of age, is associated both with a poorer clinical outcome than the onset before 18 and with a longer delay before the first treatment for mania and depression (Perlis et al., 2009; Post et al., 2010).

Widespread neuropsychological deficits in relation to attention, working memory, executive functions, and verbal memory and learning have repeatedly been described in patients with EOBD (Doyle et al., 2005; Joseph et al., 2008; Karakurt et al., 2013; Lera-Miguel et al., 2011; Nieto and Castellanos, 2011; Udal et al., 2012). Moreover, medium effect sizes have also been observed on lower performance of EOBD in verbal fluency, visual perceptive skills, and visual memory, compared to healthy controls (HC), as well as more consistent impairments. The presence of psychotic symptoms and a longer treatment with mood stabilizers have been related to the most severe cognitive deficits in adult populations with BD (Martinez-Aran et al., 2008; Gualtieri and Johnson, 2006; Holmes et al., 2008). Similar evidence has been recruited about the cognitive

* Correspondence to: Department of Child and Adolescent Psychiatry and Psychology. Hospital Clínic. C/Villarroel, 170, 08036 Barcelona, Spain.
Tel.: +34 932279974; fax: +34 932279172.
E-mail address: slera@clinic.ub.es (S. Lera-Miguel).

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impairment related to psychotic symptoms in children and adolescents (Arango et al., 2014; Zabala et al., 2010). These data raise questions that need additional study in EOBD populations.

The search is now underway for a common cognitive impairment for individuals with EOBD, adults with BD and their relatives (Cahill et al., 2009; Bora et al., 2009). Young adults with BD have shown impairment in executive functions during adolescence before the first appearance of the illness, as reflected in lower scores on the Wisconsin Card Sorting Test (Meyer et al., 2004). Studies with patients and relatives show common deficits in working memory, visual memory, and executive functions, while the role of verbal memory is inconsistent (Doyle et al., 2009; Frangou et al., 2005). Previous longitudinal studies have documented the maintenance of cognitive deficits for some years in adult patients with BD (Samamé et al., 2014; Santos et al., 2014). Long-term follow-up studies of young patients with BD are also needed to confirm the presence of permanent, specific deficits.

Very few studies have compared the course of neurocognition in treated child and adolescents with BD. In the short term, adolescents and young adults medicated with aripiprazole for 24 weeks improved in sustained attention and cognitive flexibility (Wang et al., 2012). Children treated with lamotrigine for 14 weeks have also shown improvement in working memory and verbal memory, although deficits in attention and executive functions persisted in comparison with healthy controls (Pavuluri et al., 2010). To our knowledge, only one study has reported longer-term outcomes for neuropsychological performance in treated children with EOBD, finding an overall improvement in most cognitive functions, particularly in attention tasks; however, the performance of EOBD subjects lagged behind that of HC three years after baseline (Pavuluri et al., 2009).

The main aim of this study was to increase knowledge about the course of neurocognitive function in adolescents with EOBD, assessing their performance in a wide battery of neuropsychological tests at two points in time, separated by more than two years of treatment. We focused on the comparison between euthymic states of adolescents diagnosed as type I or II BD in contrast with a control sample of healthy adolescents. Our secondary aim was to observe the influence on cognitive performance, during follow-up, of the presence of psychotic symptoms and the different outcome due to mood-stabilizer treatment (lithium or valproate). Our hypotheses were: (a) EOBD individuals would improve their performance in attention, working memory, and verbal memory from baseline to follow-up; (b) EOBD individuals would continue to show deficits in executive functions; (c) the EOBD neuropsychological profile would be worse than the HC profile; (d) patients with psychotic symptoms would show a worse cognitive outcome than patients without; and (e) no differences would be observed between lithium and valproate.

2. Methods

This is a naturalistic, prospective, and controlled study of the cognitive outcomes of a sample of treated adolescents with EOBD. Preliminary results of baseline data of a portion of the sample have previously been published (Lera-Miguel et al., 2011).

2.1. Sample

Twenty adolescents with a diagnosis of EOBD, type I or type II, were recruited for this follow-up study, part of a wider-ranging study on the clinical and neuropsychological characteristics of EOBD patients and their relatives. All patients started naturalistic pharmacological treatment between 2007 and 2009 and were followed for at least two years, at the Department of Child and Adolescent Psychiatry and Psychology, Hospital Clínic, Barcelona, Spain. The diagnosis was established according to DSM-IV criteria and treatment was applied following internal guidelines, based on the recommendations of the American Academy of Child and Adolescent Psychiatry (McClellan et al., 2007). Neuropsychological evaluation was carried out once euthymia had been guaranteed for one to three months. The re-test sample was recruited from participants who had been diagnosed and had been in treatment for at least two years. From 25 subjects in that situation, 20 agreed to be re-evaluated, three declined, one could not be contacted and another was in an unstable state due to drug abuse and was removed from the study. The inclusion criteria included: type I or II diagnosis of BD, age between 12 and 17 years old, beck depression inventory raw score <18, young mania rating scale raw score <8. The exclusion criteria included: no otherwise specified forms of BD, schizoaffective disorders, eating disorders patients in low weight (body mass index <17), drug dependence disorder or current abuse, psychosis induced by drugs, autism spectrum disorders, organic or neurologic diseases, and mental retardation.

Twenty healthy adolescents were recruited from another study conducted in the same department at the same time and formed the control group. Healthy controls (HC), matched for gender and age with the EOBD sample, were selected from that study and asked to participate in our study in order to retest the same neurocognitive functions.

Both assessments of patients and controls were done between 2007 and 2011. All patients and parents gave informed consent to participate. Healthy controls also received financial compensation for their participation. Institutional Review Boards of Hospital Clinic approved the project.

Table 1 includes baseline clinical data for the EOBD sample. Forty percent of patients came from upper or middle–upper socioeconomic status, another 40% from middle class and the remaining

Table 1
Clinical data of EOBD sample at baseline.

	N (%)	Mean (sd)
DSM-IV-TR diagnosis at recruitment		
Bipolar disorder type I	18 (90%)	
Bipolar disorder type II	2 (10%)	
Comorbidity	5 (25%)	
Externalizant (ADHD/substance abuse/opossitional defiant)	4 (20%)	
Internalizant (obsessive-compulsive disorder)	1 (5%)	
Type of first episode		
Manic/hypomanic	8 (40%)	
Depressive	3 (15%)	
Mixed/unspecified	9 (45%)	
Duration of illness > 1 year	5 (25%)	
Previous hospitalizations	16 (80%)	
One	7 (35%)	
Two or more	9 (45%)	
Suicidal ideation/suicide attempts	4 (20%)/1(5%)	
Psychotic symptoms	6 (30%)	
Drug therapies		
Mood-stabilizers monotherapy	2 (10%)	
Combined therapy	18 (90%)	
Anticonvulsivants/mood-stabilizers	20 (100%)	
Atypical antipsychotics	17 (85%)	
Antidepressants	3 (15%)	
Age at onset of first unspecified symptoms		12.9 ± 2.6
Age at onset of specified BD symptoms		14.1 ± 2.2
YMRS score		1.5 ± 1.8
BDI score		9.3 ± 5.9