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Distinguishing prodromal stage of bipolar disorder and early onset schizophrenia spectrum disorders during adolescence

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ABSTRACT

Prodromal symptoms of bipolar disorder (BD) and early onset schizophrenia spectrum disorder (EOSSD) overlap. To date, there has been no study directly comparing the prodromal stage of both disorders. Thus, the current study is aimed at determining which prodromal symptom clusters differentiate BD and EOSSD. One hundred twenty one adolescents (33 BD-1, 30 EOSSD, 58 healthy controls) were evaluated for the presence of 79 prodromal symptoms, divided into 7 prodromal symptom clusters. Great than 2 subsyndromal manic symptoms and ADHD comorbidity were significantly more specific for BD than schizophrenia; brief limited intermittent psychotic symptoms (BLIPS) were more likely to be part of EOSSD. In contrast, attenuated psychotic symptoms, and negative symptoms were not specifically related to the diagnosis of EOSSD. In conclusion, subsyndromal manic symptoms, BLIPS, and ADHD might be useful for predicting the trajectory of an emerging affective disorder versus schizophrenia and thus valuable for early detection, and intervention strategies.

1. Introduction

Bipolar disorder (BD) and early-onset schizophrenia (EOS) are severe, chronic, and recurrent psychiatric disorders that cause high rates of hospitalization, suicide attempts, substance abuse, and psychiatric comorbidity (Birmaher, 2007; McClellan and Stock, 2013). Therefore, EOS and BD are ranked as the second- and fourth-leading causes of disability-adjusted life-years in 15- to 19-year-old adolescents worldwide, respectively (Gore et al., 2011).

A prodrome is a symptom that precedes a full diagnosis. The prodromal stage is an important target in terms of preventing an ailment, delaying the first episode, hindering psychiatric comorbidity, and alleviating the severity of the disorder (Bechdolf et al., 2012). Interventions that are less complex and more tolerable (e.g., psychotherapy, monotherapy) than those that are instituted in the later periods (e.g., multidrug treatment) can be effective during the prodromal stage. In addition, early interventions may even have a better treatment impact during this period than in later stages of the disorder (Vieta et al., 2018).

Several studies have investigated the prodromal stage of schizophrenia and related psychotic disorders as well as BD (Larson et al., 2010; Skjelstad et al., 2010). The most prevalent prodromal symptoms in schizophrenia include social isolation, academic difficulties, anxiety symptoms, odd behaviors, and depressive symptoms (Keshavan et al., 2011). The most commonly reported prodromal symptoms in BD are irritability, sleep disturbances, hyperactivity, anxiety, and subsyndromal manic/depressive symptoms (Howes and Falkenberg, 2011; Skjelstad et al., 2010).

A good number of studies have reported that BD and schizophrenia share aspects of phenotypical, genetic, and neurobiological pathophysiology (Bora et al., 2009; Bora and Pantelis, 2016; Cardno and Owen, 2014; Chen et al., 2018; Hollander et al., 2016). Moreover, mania and schizophrenia prodromes have substantial overlap in both symptom expression and onset patterns (Correll et al., 2007). However, little

Abbreviations: EOS, Early onset schizophrenia; EOSSD, Early onset schizophrenia spectrum disorder; BD, Bipolar disorder; CG, Control group; UHR, Ultra high risk; K-SADS-PL, Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version; CGAS, Children's global assessment scale; PAS, Premorbid adjustment scale; HDRS, Hamilton depression rating scale; YMRS, Young mania rating scale; PANNS, Positive and negative syndrome scale; BLIPS, Brief limited intermittent psychotic symptoms; APS, Attenuated psychotic symptoms; ERIraos, Early recognition inventory, interview for the retrospective assessment of the onset and course of schizophrenia and other psychoses.; BPSS-R, Bipolar prodrome symptom scale-retrospective

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research to date has focused on distinguishing the prodromal stage of EOS and BD. Correll et al. (2007) presented the first data on the differentiation of the preonset phases of schizophrenia and mood disorders. They found that obsessions/compulsions, suicidality, difficulty thinking/communicating clearly, depressed mood, decreased concentration/memory, tiredness/lack of energy, mood lability, and physical agitation were more specific to a mania prodrome, although subsyndromal unusual ideas were more likely to be part of a psychosis prodrome. In their study, they recruited youths with BD and compared their prodromal symptoms with subjects in the literature. From the literature, they chose three different retrospective studies investigating the prodromal symptoms of adults with schizophrenia. These studies had used diverse methods to examine the prodromal stage. Thus, in their conclusions, the authors recommended that studies using the same methodology to assess patient groups are needed to verify any substantial overlap or isolated differences between the prodrome of psychosis and BD. For this reason, our study directly compared the prodromal stage of adolescents with early-onset schizophrenia spectrum disorders (EOSSD) and BD, after a careful confirmation of their diagnosis.

Given the shared underlying biological basis, one disorder might evolve into another at a later time (e.g., an adolescent diagnosed with BD may convert to schizophrenia in adulthood) (Mcgorry et al., 2018). Consistent with this, only one in three individuals at ultra high risk (UHR) for psychosis converts to psychosis within 3 years (Schmidt et al., 2015). Approximately a third of UHR individuals transform into nonpsychotic disorders (Lim et al., 2015a,b; Wigman et al., 2012). In addition, individuals at risk for nonpsychotic disorders (depressive disorder, BD, obsessive compulsive disorders) may convert to psychosis (Lee et al., 2018; Mcgorry et al., 2018). This situation might also be valid for the early stage of BD. Patients with attention-deficit hyperactivity disorder (ADHD), substance use disorders, anxiety disorders, major depressive disorders, or individuals at UHR for psychosis are at elevated risk for BD (Brietzke et al., 2012; Faedda et al., 2014). Therefore, the early stage of a mental disorder has a dynamic presentation with diffuse symptom patterns and transdiagnostic trajectory (Mcgorry et al., 2018; Vieta et al., 2018).

To the best of our knowledge, there is no study directly comparing the prodromal stage of EOSSD and BD during adolescence. The first aim of the present work is to distinguish the prodromal stage of BD and EOSSD during adolescence. The second aim is to identify the prevalence of subgroups that have different trajectories within the prodromal stage (e.g., subgroup of BD experiencing psychotic symptoms in prodrome). We hypothesize that (1) attenuated psychotic symptoms (APS), negative symptoms, and brief limited intermittent symptoms (BLIPS) would be more specific to EOSSD prodrome; (2) subsyndromal manic symptoms would be more specific to the prodrome of BD; and (3) there would be some subgroups experiencing psychotic prodromal symptoms in the BD group and affective-type prodromal symptoms in the EOSSD group.

2. Methods

2.1. Subject recruitment

A power analysis was applied (alpha 0.05, power of 0.85, 1:1 ratio) to calculate the minimum sample size for EOSSD and BD. The expected prevalence of prodromal symptoms was determined based on the finding of strange or unusual ideas at the prodromal stage in 53.3% of patients with schizophrenia and 16.7% of patients with BD (Jackson et al., 1995). A minimum sample size of 29 subjects in each group was determined. One hundred sixty patients being followed up between November 2006 and November 2017 at Ege University School of Medicine Adolescent Unit of Department of Child and Adolescent Psychiatry with the diagnosis of EOSSD or BD were evaluated in terms of inclusion and exclusion criteria. Inclusion criteria for BD were (a) age between 13 and 19 years and (b) BD type 1 according to DSM-IV. Inclusion criteria for EOSSD were (a) age between 13 and 19 years and (b) EOSSD according to DSM-IV. Exclusion criteria for BD and EOSSD included (a) parents or guardians who were unable or unwilling to provide consent, (b) diagnosis of intellectual disability and/or autism spectrum disorder, (c) neurological and/or chronic medical disorder, and (d) substance-induced BD or EOSSD. Psychopathology was assessed via the Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version (K-SADS-PL), based on DSM-IV. Eighty-three patients were excluded. Afterward, one of the authors (T.B.) interviewed the remaining patients ($n = 77$). To verify the diagnosis and to determine the first full psychotic/manic episode, the summaries of the patients' files, the results of the K-SADS-PL evaluation, the Positive and Negative Syndrome Scale (PANNS) for EOSSD, and life charts for BD were presented to a jury consisting of two child and adolescent psychiatrists and one adult psychiatrist, who had also been working with adolescents since 2003. A patient was excluded if there was a disagreement between the members of the jury with regard to the diagnosis. Eventually, thirty-three patients with BD type 1 and 30 patients with EOSSD (28 with EOS, 2 schizoaffective disorder, bipolar type) were recruited for the study. Of the BD group, 36.4% ($n = 12$) had a history of psychosis. The participant selection procedure is demonstrated in Fig. 1.

We determined the frequency of prodromal symptoms in healthy nonclinical adolescents as a control group (CG). Inclusion criteria for the CG were (1) age between 13 and 19 years and (2) patient and parent were willing and able to give informed consent. The exclusion criterion for the CG was the presence of any psychiatric disorder or chronic medical disease. Subjects were chosen by modified systematic random sampling from three secondary schools and three high schools in Izmir Province. Fifty-eight healthy adolescents were enrolled in the CG. The detailed selection process for the CG is provided as supplemental material.

2.2. Assessment and materials

A sociodemographic data form, K-SADS-PL, Children's Global Assessment Scale (CGAS), Premorbid Adjustment Scale (PAS), Hamilton Depression Rating Scale, and Young Mania Rating Scale (YMRS) were administered to each group (EOSSD, BD, and CG). In addition, a life chart, which demonstrates all mood episodes, symptoms during episodes, psychopharmacological treatments and side effects, and life events related to mood episodes, was created for each adolescent with BD to aid in the diagnosis. The PANNS was calculated for evaluating the current symptoms of EOSSD. We composed a sociodemographic data form evaluating the characteristics of children (age, gender, educational status) and sociodemographic features of their families (parental marriage status, psychiatric disorder in family, education level of parents). The K-SADS-PL was used both to confirm the diagnosis and to detect comorbid psychiatric disorders (Gökler et al., 2004; Kaufman et al., 1997). The CGAS and PAS were rated to appraise the present and premorbid functioning, respectively (Cannon-Spoor et al., 1982; Shaffer, 1983). Patients who were in active manic episode and psychotic episode were excluded (YMRS score of >8).

The PAS measures the levels of functioning on four domains, which consist of social accessibility-isolation, peer relationship, ability to function outside the nuclear family (school performance and adaptation to school), and capacity to establish social-sexual relationships. Each domain is outlined in childhood (up to 11 years), early adolescence (12–15 years), late adolescence (15–18 years), and adulthood. The higher the PAS score rates, the lower the level of functioning. The social-sexual relationship domain was not implemented in our study because it was not culturally appropriate. Since the questionnaire was carried out from 1 year before the first full episode, the period of adulthood was not questioned either.

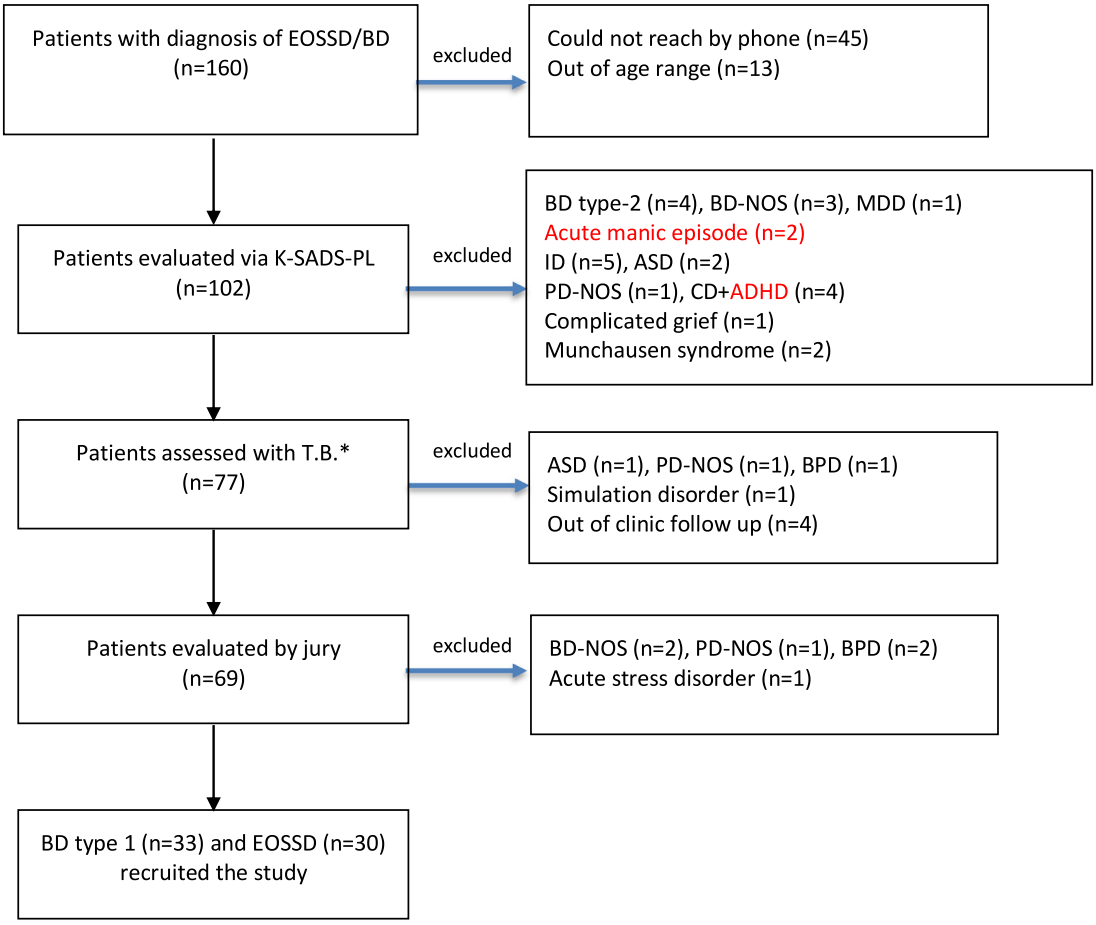

Fig. 1. Flow diagram for participant selection.
* Tezan Bildik, EOSSD = early onset schizophrenia spectrum disorder, BD = bipolar disorder, PD = Psychotic disorder, KSADS-PL = Schedule for Affective Disorders and Schizophrenia for School Aged Children, Present and Lifetime Version, NOS = not otherwise specified, MDD = major depressive disorder, ID = intellectual disability, ASD = autism spectrum disorder, CD = conduct disorder, BPD = borderline personality disorder, ADHD = attention deficit hyperactivity disorder.

2.3. Inquiring of the prodromal stage

To investigate the prodromal stage of BD and EOS, a modified, semistructured, clinician-rated interview was formed. It was based on two instruments, including the Bipolar Prodrome Symptom Scale–Retrospective and the Early Recognition Inventory, Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses (ERIraos) (Correll et al., 2014; Maurer et al., 2006). Prodromal symptoms described in these studies were compounded. Seventy-nine symptoms were thus divided into seven groups: general psychopathology symptoms, negative symptoms, basic symptoms, BLIPS, APS, subsyndromal manic symptoms, and subsyndromal depressive symptoms. The first full psychotic/manic episode was determined at the jury meetings. After that, the clinician (H.Y.K.) queried all 79 prodromal symptoms separately by asking if the individual had experienced the relevant symptoms in the 3 years prior to the first full psychotic/manic episode. The CG was questioned regarding the 3 years before the interview (e.g., in the past 3 years, have you felt that thoughts are sometimes withdrawn from your head?).

In the case of the presence of any prodromal symptom, the duration before the first episode and deterioration during the prodromal stage were inquired. For CG, the duration before the interview for each symptom was noted. Distress associated with the symptom (1 = not distressful, 2 = distressful, 3 = very distressful) and the frequency of the symptom (1 = sometimes, 2 = often, 3 = nearly always, 4 = lifelong, temperament) were measured. Only distressful and very distressful symptoms were included in the study. Worsening of symptoms was determined by at least a 1-point increase in symptom severity or frequency of relevant symptom within 3 years. Symptoms that were stable or lifelong were excluded. The onset of prodromal stage was described as new onset/worsening symptoms within 3 years before the first full episode. In addition, based on the literature, the onset pattern of the prodrome was defined as "gradual onset as ≥ 4 months and rapid onset as < 4 months," and the deterioration pattern was identified as "slow deterioration as ≥ 4 weeks and rapid deterioration as < 4 weeks" (Correll et al., 2014).

The definitions of basic symptoms, APS, and BLIPS were based on the ERIraos (Maurer et al., 2006). According to the ERIraos, declaring the symptoms is enough for APS or basic symptoms (Maurer et al., 2006). For BLIPS, symptoms must last fewer than 7 days and remit spontaneously. In addition, there has to be at least 1 week without psychotic symptoms between two BLIPS episode (Maurer et al., 2006).

2.4. Statistical analysis

Descriptive statistics were used to define sample characteristics, duration of prodromal stage, and frequency of the prodromal symptom clusters (≥1, ≥2, ≥3, ≥4, ≥5 general symptoms; ≥1 APS; ≥1 BLIPS; ≥1 basic symptoms; ≥1 and ≥2 negative symptoms; ≥1, ≥2, ≥3 subsyndromal manic and depressive symptoms). Because of the very limited sample size in each group ($n < 5$), ≥2 APS, ≥2 BLIPS, and ≥2 basic symptoms were not reported. Between-group comparisons of

categorical variables were carried out using χ^2 or Fisher's exact test. Independent-sample *t*-test was used to compare EOSSD and BD in terms of mean age at first admission to a psychiatry clinic and the mean age at diagnosis. Analysis of variance was applied to analyze the difference in number of prodromal symptoms and total PAS score between all groups (EOSSD, BD, CG). For nonnormally distributed continuous variables, Mann-Whitney *U* test and Kruskal–Wallis test were applied for comparison of the variables between the two groups (EOSSD, BD) and three groups (EOSSD, BD, CG), respectively. Bonferroni-adjusted alpha level ($p = 0.0166$) was used in the Kruskal–Wallis post hoc pairwise comparison. Logistic regression analysis was performed to detect which prodromal symptom clusters were predictive for distinguishing BD from EOSSD. Latent class analysis was implemented to all of the study population via R software with the package of Mclust to define the subgroup of the patients who could be allocated from each other in terms of prodromal symptoms (number of positive items for psychotic, manic, depressive, and nonspecific symptoms). Avoiding preassumption of the number of patients in the subgroups, Bayesian information criterion (BIC) values were used to achieve the best cluster modeling. Data were analyzed by IBM SPSS version 17.0 for Mac, except for the cluster analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated, and upper and lower limits were reported. Statistical significance was set at $\alpha < 0.05$.

3. Results

3.1. Sample and illness characteristics

Although the mean age of patients in the EOSSD, BD, and CG groups were similar, the distribution of sex was statistically different (Table 1). Females were more predominant in the BD and EOSSD groups. As shown in the Table 1, the educational level of parents did not differ between the groups, although the divorce rate was highest in the BD group. Forty percent of patients in the BD and EOSSD groups had a family history of bipolar disorder and psychosis, respectively.

At the time of the interview, patients with BD had experienced 3.3 (SD = 1.7) mood episodes, and patients with EOSSD had experienced 1.5 (SD = 1.9) psychotic episodes. The index mood episode was depressive episode in 51.5% of adolescents with BD. No significant differences in the mean age at first admission to a psychiatry clinic, the mean age at diagnosis, or lag between the first episode and diagnosis of EOSSD/BD were found between the EOSSD and BD groups ($p > 0.05$; Table 2). On the other hand, the duration of disorder, defined as a lag between the first episode and the date of the interview, was longer in BD than in EOSSD ($p = 0.036$). As demonstrated in Table 2, the percentage of psychiatric comorbidity was higher in the BD (81.8%) than in the EOSSD (56.7%) group ($p = 0.030$).

The prevalence of ADHD, the most frequent psychiatric comorbidity in the BD group along with anxiety disorder, was statistically significant between the two groups ($p = 0.003$). Remission rates and functionality (CGAS) were better in the BD group than in the EOSSD group (for remission, $p = 0.041$; for CGAS score, $p < 0.001$; Table 2). For both EOSSD and BD, gradual onset (≥4 months) with slow deterioration (≥1 month) were the leading onset and deterioration patterns of the prodromal stage (Table 2). There was no significant difference between psychotic BD and nonpsychotic BD in terms of onset and deterioration pattern of the prodromal stage ($X^2 = 4.411$, $p = 0.121$).

3.2. Premorbid adjustment

The total score of the PAS was calculated as 0.24 (SD = 0.11; 95% Cl = 0.20–0.29) for EOSSD, 0.27 (SD = 0.15; 95% Cl = 0.21–0.32) for BD, and 0.08 (SD = 0.06; 95% CI = 0.06–0.010) for CG, $F(2) = 37.21$, $p < 0.001$. Although the total score of the PAS was significantly higher in the BD and EOSSD groups than in the CG ($p < 0.001$), there was no significant difference between EOSSD and BD groups ($p = 1.000$) according to Bonferroni post hoc analysis test. In addition, the childhood sections of the PAS including sociality, peer relationships, academic functioning, and adaptation (behavioral functioning) were not significantly different between the EOSSD and BD groups according to Kruskal–Wallis post hoc pairwise comparison ($p > 0.0166$).

Table 1
Socio-demographic variables of the groups.

	BD (*N* = 33)		EOSSD (*N* = 30)		CG (*N* = 58)			
	n	%	*n*	%	*n*	%	X^2 (*df*)[a]	*p value*
Gender								
Female	28	84.8	18	60	25	43.1	15.14 (2)	0.001*
Male	5	15.2	12	40	33	56.9		
Mother's education								
Illiterate	1	3	4	13.3	7	12.1	15.44 (8)	0.051
Primary school	16	48.5	15	50	13	22.4		
Secondary and High School	9	27.3	10	33.3	23	39.6		
Collage	7	21.2	1	3	15	25.9		
Father's education								
Illiterate	2	6.2	1	3.3	5	8.6	14.12 (–)	0.059
Primary school	13	39.4	12	40	9	15.5		
Secondary and High School	13	39.4	13	43.4	23	36.7		
Collage	5	15.1	4	13.4	21	36.4		
Parent's marital status								
Divorced	12	36.4	3	10	5	8.6	12.96 (2)	0.002*
Psychiatric disorder in family	30	90.9	22	73.2	10	17.2	53.479(2)	<0.001*
Bipolar disorder in family	13	39.4	2	6.7	1	1.7	23.458 (–)	<0.001*
Psychosis in family	8	24.2	12	40	1	1.7	23.935 (–)	<0.001*
	Mean	SD	Mean	SD	Mean	SD	*H* (*df*)[b]	*p value*
Age	16.7	1.4	16.3	1.8	15.9	1.7	4.415 (2)	0.110
Number of family members	3.6	1	4.5	1.2	4.1	1.1	6.52(2)	0.038*

[a] Chi Square.
[b] Kruskal Wallis.
* $p < 0.05$, SD = standard deviation, BD: bipolar disorder, EOSSD: early onset schizophrenia spectrum disorder, CG: control group.
Description of Table 1: The sociodemographic features of each group is demonstrated.

Table 2
Illness characteristics and psychiatric comorbidity in the study groups (EOSSD and BD).

	EOSSD (N = 30) Mean	SD	BD (N = 33) Mean	SD	Statistics t, U	p value
First psychotic episode (Years)	14.8	1.8	n.a.	n.a.	n.a.	n.a.
First hypo(manic) episode (Years)	n.a.	n.a.	15	1.5	n.a.	n.a.
First depressive episode (Years)	n.a.	n.a.	14.4	1.9	n.a.	n.a.
First admission to psychiatry (Years)	13.9	3.2	12.8	4.4	−1.70	0.286[a]
Age at diagnosis of BD/EOSSD (Years)	15	1.7	15.3	1.6	0.75	0.456[a]
Duration of disorder (Months)	20.2	15.2	31.5	21.8	343	0.036[b]
Lag between first episode and diagnosis of BD/EOSSD (Months)	4.21	10.7	6.14	9	450.5	0.687[b]
Total PANNS Score						
At first episode	56	29.3	n.a.	n.a.	n.a.	n.a.
Current	30	16.3	n.a.	n.a.		
Hamilton Depression Rating Scale	3.4	3.6	4.6	4.8	437	0.414[b]
Young Mani Rating Scale	2.2	3.9	4.9	5.0	304.5	0.006[b]

	n	%	n	%	$\chi 2$	P value
Psychiatric comorbidities	17	56.7	27	81.8	4.720	0.030[c]
ADHD	7	23.3	21	63.6	8.770	0.003[c]
Anxiety disorder	12	40	21	63.6	2.636	0.104[c]
Oppositional defiant disorder	0	0	6	18.2		0.025[c]
Conduct disorder	0	0	3	9.1		0.240[c]
Remission rates						
Full remission	7	23.3	17	51.5	4.164	0.041[c]
Partial remission	23	76.7	16	48.5		
CGAS Score						
<40	22	73.3	7	21.2	17.116	<0.001[c]
40–70	4	13.3	18	54.5		
>70	4	13.3	8	24.2		
Onset and deterioration of prodrome						
Gradual onset & slow deterioration	12	40	21	63.6	3.574	0.192[c]
Gradual onset & rapid deterioration	11	36.7	7	21.2		
Rapid onset & rapid deterioration	7	23.3	5	15.2		

[a] Independent sample t-test.
[b] Mann Whitney U test.
[c] Chi Square test/Fisher's exact test, SD = standard deviation, 95%CI = 95% confidence intervals, n.a. = not applicable, BD: bipolar disorder, EOSSD: early onset schizophrenia spectrum disorder, PANNS: Positive and negative syndrome scale, ADHD: attention deficit and hyperactivity disorder.

Description of Table 2: The illness characteristics and psychiatric comorbidities are illustrated.

3.3. Duration of the prodromal stage

In the EOSSD and BD groups, 98.3% and 94% of patients, respectively, had at least one prodromal symptom before their first episode, and 80% of the EOSSD and 87.9% of the BD group had at least five prodromal symptoms before their full episode. The duration of the prodromal stage was 22.6 (SD = 12.6; 95% CI = 18.7–27.8) months for EOSSD and 26.3 (SD = 10; 95%CI = 22.7–29.9) months for BD (U = 421, p = 0.304). The prodromal stage was longer than a year in 73.4% and 87.9% of adolescents with EOSSD and BD, respectively. The mean age of onset of the prodromal stage was 12.9 (SD = 1.8) in the EOSSD group and 13 (SD = 1.9) in the BD group. The duration of the prodromal stage did not significantly differ between psychotic BD (22.3 [SD = 10.4]) and nonpsychotic BD (28.6 [SD = 9.2]) (U = 76, p = 0.063).

3.4. Prevalence of prodromal symptoms

The number of prodromal symptoms reported before the full episode was 10 (SD = 7.4; 95% CI = 7.2–12.8) in the EOSSD group and 12.7 (SD = 7.2; 95% CI = 10.1–15.3) in the BD group. The average number of prodromal symptoms in the CG was 2 (SD = 2.1; 95% CI = 1.4–2.5). Significant differences in the number of prodromal symptoms were found between the groups, $F(2, 118) = 46.561$, $p < 0.001$.

Most of the prodromal symptoms were significantly more frequent in the EOSSD and BD groups than in the CG ($p < 0.05$), except for ruminations, social phobia, tension/restlessness, obsessions/compulsions, ambivalence, unusual thought content, and overtalkativeness ($p > 0.05$; Table 3). When we compared EOSSD and BD, significant differences were detected only for the following prodromal symptoms: extreme energy (p = 0.013, OR = 12.6, 95% CI = 1.5–105.8), inflated self-esteem (p = 0.039, OR = 12.6, 95% CI = 1.5–105.8), impulsivity (p = 0.021, OR = 7, 95% CI = 1.4–34.9), suicidal thoughts (p = 0.009, OR = 6.6, 95% CI = 1.6–26.3), sleeplessness (p = 0.026, OR = 4.5, 95% CI = 1.1–18.1), oppositionality (p = 0.02, OR = 4.2, 95% CI = 1.3–13), and temper tantrums (p = 0.032, OR = 3.3, 95% CI = 1–10.2). On the other hand, the prevalence of suspiciousness was more frequent in the prodromal stage of EOSSD (p = 0.005, OR = 11.96, 95% CI = 1–10.7).

The prevalence of all prodromal symptom clusters was significantly higher in the EOSSD and BD groups than in the CG ($p < 0.05$; Fig. 2). Compared with EOSSD, adolescents with BD were more likely to have ≥1 subsyndromal manic symptoms (OR = 4.26, 95% CI = 2.1–8.3), ≥2 subsyndromal manic symptoms (OR = 3.08, 95% CI = 1.7–5.4), and ≥3 subsyndromal manic symptoms (OR = 7.5, 95% CI = 1.8–29.6); ≥1 subsyndromal depressive symptoms (OR = 2.2, 95% CI = 0.5–8.4), ≥2 subsyndromal depressive symptoms (OR = 3, 95% CI = 1–8.7), and ≥3 subsyndromal depressive symptoms (OR = 2.7, 95% CI = 0.9–7.5) in the prodromal stage. However, the frequencies of ≥1 negative symptoms (OR = 1.3, 95% CI = 0.5–93.6), ≥2 negative symptoms (OR = 2.75, 95% CI = 0.8–9.4), ≥1 basic symptoms (OR = 1.76, 95% CI = 0.6–4.9), ≥1 APS (OR = 2.47, 95% CI = 0.8–7.5), and ≥1 BLIPS (OR = 4.96, 95% CI = 0.8–24.8) were at least 1.3 times as high in the EOSSD group than in the BD group. Among prodromal symptom clusters, the prevalence of ≥1 subsyndromal manic symptoms ($X^2[1] = 5.989$, p = 0.014), ≥2 subsyndromal manic symptoms ($X^2[1] = 4.751$, p = 0.029), ≥3 subsyndromal manic

Table 3
Comparison of the prevalence and duration of the prodromal symptoms between the groups.

	BD (*N* = 33)			EOSSD (*N* = 30)			CG (*N* = 58)		Comparison of EOSSD-BD-CG	
	n	%	Duration (Mean ± SD) (Months)	*n*	%	Duration (Mean ± SD) (Months)	*n*	%	X^2	*p value*[a]
≥1 General symptom	32	97		27	90		34	58.6	23.775	<0.001*
Oppositionality	17	51.5	18.5 ± 6.5	6	20	17.6 ± 7.6	2	3.4	30.142	<0.001*
Decreased school functioning	17	51.5	17.9 ± 9.3	14	46.7	12.21 ± 13.1	8	13.4	18.411	<0.001*
Reduced school attendance	15	45.5	15.66 ± 9.8	15	50	13.4 ± 10.2	n.a.	n.a.	44.855	<0.001*
Temper tantrums	15	45.5	15.3 ± 8.5	6	20	14 ± 10.9	n.a.	n.a.	32.915	<0.001*
Mood lability	14	42.4	18.5 ± 10	9	30	15.11 ± 1.4	3	5.2	20.672	<0.001*
İnitial İnsomnia	11	33.3	17 ± 9.5	8	26.7	18.8 ± 12.4	4	6.9	11.779	0.003*
Sleeplessness	11	33.3	15.1 ± 9	3	10	9 ± 10.4	1	1.7	17.967	<0.001*
Deterioration in peer relationships	7	21.2	20 ± 11	12	40	21.08 ± 13.5	1	1.7	22.752	<0.001*
Ruminations	8	24.2	17.8 ± 8.2	8	26.7	18.2 ± 10.9	9	15.5	1.870	0.393
Tension/restlessness	6	18.2	16.7 ± 18	8	26.7	17 ± 14.4	9	15.5	1.544	0.462
Inappropriate affect	7	21.2	22.1 ± 14	8	26.7	14.12 ± 12.4	2	3.4	11.558	0.003*
Worries (also about mental function)	6	18.2	20.1 ± 9.2	7	23.3	16.5 ± 11.3	1	1.7	12.049	0.002*
Waking from nocturnal sleep	3	9.1	14 ± 7.8	1	3.3	n.a.	1	1.7	2.702	0.244
Decreased sexual desire	2	6.1	22.5 ± 2.1	1	3.3	n.a.	n.a.	n.a.	3.407	0.138
Odd behavior	2	6.1	7.3 ± 6.3	4	13.3	18.2 ± 12.1	n.a.	n.a.	7.436	0.013*
Social phobia	5	15.2	27.5 ± 7.7.	4	13.3	8.4 ± 4	4	6.9	1.993	0.408
Obsessions and compulsions	3	9.1	19.2 ± 5.2	4	13.3	11.6 ± 10.6	5	8.6	0.669	0.736
Increased appetite	1	3	n.a.	2	6.7	22	1	1.7	1.693	0.368
Loss of appetite	3	9.1	16.6 ± 17	4	13.3	17 ± 15.8	n.a.	n.a.	8.072	0.007
Hypersomnia	1	3	n.a.	1	3.3	n.a.	1	1.7	0.831	1.000
Ambivalence	4	12.1	14.5 ± 7.1	4	13.3	21 ± 12.6	12	20.7	1.251	0.566
Overvalued ideas	n.a	n.a.	n.a.	3	10	10.3 ± 9.4	1	1.7	4.219	0.098
Disturbed diurnal rhythm	4	12.1	15 ± 7.8	3	10	19.6 ± 16.5	1	1.7	4.805	0.077
≥1 Negative Symptoms	15	45.5		16	53.5		4	6.9	29.518	*P* < 0.001*
Social withdrawal	12	36.4	18.8 ± 11.5	11	36.7	15.81 ± 1.8	1	1.7	27.746	<0.001*
Decreased ability to maintain or initiate social contacts	5	15.2	18.2 ± 9.9	10	33.3	14.9 ± 7.8	1	1.7	17.228	<0.001*
Flat affect	3	9.1	14.3 ± 6.8	6	20	10.8 ± 7.8	2	3.4	6.096	0.035*
≥1 Basic Symptoms	10	30.3		13	43.3		4	6.9	17.817	<0.001*
Perseveration	1	3	n.a.	3	10	22.3 ± 14.5	1	1.7	3.103	0.151
Decreased ability to discriminate between ideas and perception or fantasy and true memories	2	6.1	9.5 ± 3.5	6	20	18.5 ± 10.6	1	1.7	8.377	0.007*
Disturbance of receptive speech	2	6.1	12	2	6.7	7	n.a.	n.a.	4.269	0.070
Thought block	2	6.1	24 ± 16.9	2	6.7	21	n.a.	n.a.	4.269	0.070
Depersonalization/derealization	1	3	n.a.	1	3.3	n.a.	1	1.7	0.831	1.000
Unstable ideas of reference	1	3	n.a.	3	10	14.6 ± 18.5	1	1.7	3.101	0.151
Disturbances of visual perception	n.a	n.a.	n.a.	2	6.7	12.6 ± 8	n.a	n.a.	4.030	0.06
Disturbance of acoustic perception	n.a	n.a.	n.a.	1	3.3	n.a.	n.a.	n.a.	2.559	0.248
Disturbances of olfactory, gustatory, sensible, somatic and tactile perceptions	n.a	n.a.	n.a.	n.a	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Thought interference	7	21.2	21.8 ± 11.5	6	20	16.8 ± 12.3	2	3.4	8.923	0.010*
≥1 BLIPS[b]	2	6.1		7	23.3		n.a.	n.a.	14.034	<0.001*
Thoughts can be read	n.a.	n.a.	n.a.	5	16.7	9.6 ± 8.6	n.a.	n.a.	11.100	0.001*
Thought broadcasting	n.a.	n.a.	n.a.	2	6.7	19 ± 24	n.a.	n.a.	4.030	0.06
Delusional misinterpretation	n.a.	n.a.	n.a.	2	6.7	6 ± 1.4	n.a.	n.a.	4.030	0.06
Delusion of control	n.a.	n.a.	n.a.	1	3.3	n.a.	n.a.	n.a.	n.a.	n.a.
Delusion of persecution	1	3	n.a.	2	6.7	24	n.a.	n.a.	2.385	0.269
Delusion of jealousy	n.a.	n.a.	n.a.	1	3.3	n.a.	n.a.	n.a.	n.a.	n.a.
Grandiose delusions	n.a.	n.a.	n.a.	1	3	n.a.	n.a.	n.a.	n.a.	n.a.
Visual hallucination	1	3	n.a.	1	3.3	n.a	n.a.	n.a.	2.385	0.269
Auditory hallucination	1	3	n.a	2	6.7	8 ± 5.6	n.a.	n.a.	3.604	0.083
≥1 APS	7	21.2		12	40		3	5.2	16.642	<0.001*
Suspiciousness	1	3.3	n.a.	8	26.7	15.5 ± 14.3	2	3.4	11.736	0.001*
Ideas of reference	2	6.1	3.5 ± 2.1	5	16.7	21.2 ± 13	n.a.	n.a.	9.446	0.004*
Unusual thought contents	5	15.2	13.6 ± 9.1	3	10	16 ± 6.9	2	3.4	4.071	0.120
Abnormal perceptions	n.a	n.a	n.a.	n.a	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Bodily illusions	1	3	n.a.	n.a	n.a.	n.a.	n.a	n.a.	n.a.	n.a.
≥1 Subsyndromal Depressive Symptoms	29	87.9		23	76.7		12	22.4	48.376	<0.001*
Depressed mood	22	66.7	17.7 ± 8.4	16	55.3	18.88 ± 11.8	1	1.7	58.553	<0.001*
Suicidal thoughts	14	42.4	15.2 ± 4.6	3	10	15.3 ± 8.9	1	1.7	25.706	<0.001*
Distractibility	13	39.4	19.3 ± 9.4	10	33.3	10.09 ± 5.7	11	19	4.935	0.085
Anhedonia	13	39.4	18.6 ± 10.4	5	16.7	13.4 ± 10.7	n.a.	n.a.	27.424	<0.001*
Feeling of worthlessness	9	27.3	18.2 ± 10.2	7	23.3	13.1 ± 10.8	2	3.4	12.683	0.001*
Self-harm	9	27.3	15.2 ± 8.5	n.a	n.a.	n.a.	n.a.	n.a.	20.689	<0.001*
Tiredness	7	21.2	15.2 ± 8.3	7	23.3	12.5 ± 11.5	1	1.7	13.159	0.001*
Terminal insomnia	4	12.1	21 ± 14.5	1	3.3	n.a.	n.a	n.a.	6.793	0.013*
Reduced vitality	4	12.1	15 ± 4.2	3	10	11.3 ± 5	n.a.	n.a.	9.106	0.006*
Suicidal attempt	4	12.1	12.5 ± 4.1	1	3.3	n.a.	n.a.	n.a.	6.793	0.013*
Physical agitation	5	15.2	14.8 ± 7.3	2	6.7	6 ± 1.4	n.a.	n.a.	8.813	0.005*
≥1 Subsyndromal Manic Symptoms	28	84.8		17	56.7		20	34.5	23.220	<0.001*
Irritability	21	63.6	17.6 ± 7.2	12	40	14.8 ± 11.8	6	10.3	29.898	<0.001*

(*continued on next page*)

Table 3 (*continued*)

	BD (*N* = 33)			EOSSD (*N* = 30)			CG (*N* = 58)		Comparison of EOSSD-BD-CG	
	n	%	Duration (Mean ± SD) (Months)	*n*	%	Duration (Mean ± SD) (Months)	*n*	%	X^2	*p value*[a]
Impulsive behavior	11	33.3	14 ± 7.2	2	6.7	30 ± 8.4	n.a.	n.a.	n.a.	n.a.
Extreme energy	10	30	17.1 ± 9	1	3.3	n.a.	n.a.	n.a.	15.221	<0.001*
Inflated self esteem	10	30	17 ± 10.7	1	3.3	n.a.	3	5.2	11.356	0.002*
Over Talkativeness	6	18.2	20.5 ± 11	4	13.3	6.2 ± 3	3	5.2	4.155	0.124
Racing thoughts	7	21.2	18.7 ± 11.4	4	13.3	26.2 ± 11.8	3	5.2	8.013	0.044*
Reduced sleep requirement	5	15.2	14 ± 8.2	2	6.7	6 ± 1.4	1	1.7	5.756	0.03*
Euphoria	4	12.1	18.7 ± 13.8	n.a	n.a.	n.a.	2	3.4	4.351	0.077
Reckless behavior	3	9.1	22.6 ± 14	1	3.3	n.a.	2	3.4	1.579	0.550
Risky sexual behavior	6	18.2	14.1 ± 8	n.a	n.a.	n.a.	n.a.	n.a.	12.576	<0.001*
Increased sexual interest	8	24.2	16 ± 7.2	2	6.7	4	n.a.	n.a.	2.559	0.248
Increased creativity	5	15.2	14.8 ± 7.3	n.a	n.a.	n.a.	4	6.9	4.954	0.06

[a] Chi Square/Fisher's exact analysis.

* $p < 0.05$.

[b] BLIPS symptoms including loud thoughts, olfactory, gustatory, sensible, somatic and tactile hallucinations, delusions of reference, religious delusions, nihilistic delusions, hypo/hyperkinetic catatonic symptoms, hypochondriacal delusions did not report in any of the groups, BD: bipolar disorder, EOSSD: early onset schizophrenia spectrum disorder, CG: control group.

Description of Table 3: The prevalence and duration of the prodromal symptoms in each group are demonstrated.

symptoms ($X^2[1] = 8.020$, $p = 0.005$), and ≥1 BLIPS ($p = 0.038$) was statistically significant between the EOSSD and BD groups. The frequency of each prodromal symptom did not differ statistically between psychotic BD and nonpsychotic BD ($p > 0.05$). Only the prodromal cluster of ≥3 subsyndromal manic symptoms was significantly higher in nonpsychotic BD (61.9%) than in psychotic BD (16.7%; $X^2[1] = 6.751$, $p = 0.009$).

3.5. Distinguishing the prodromal stage of BD from EOSSD

Logistic regression analysis was employed to estimate which prodromal symptom clusters were more predictive for distinguishing the prodromal stage of BD from EOSSD. The binary logistic regression model explained 44% of the variance, and it correctly classified 76.2% of the patients, with a sensitivity of 75.8% and specificity of 76.7%. It was revealed that the presence of ≥3 subsyndromal manic symptoms ($p = 0.022$) and ADHD comorbidity ($p = 0.008$) during the prodromal

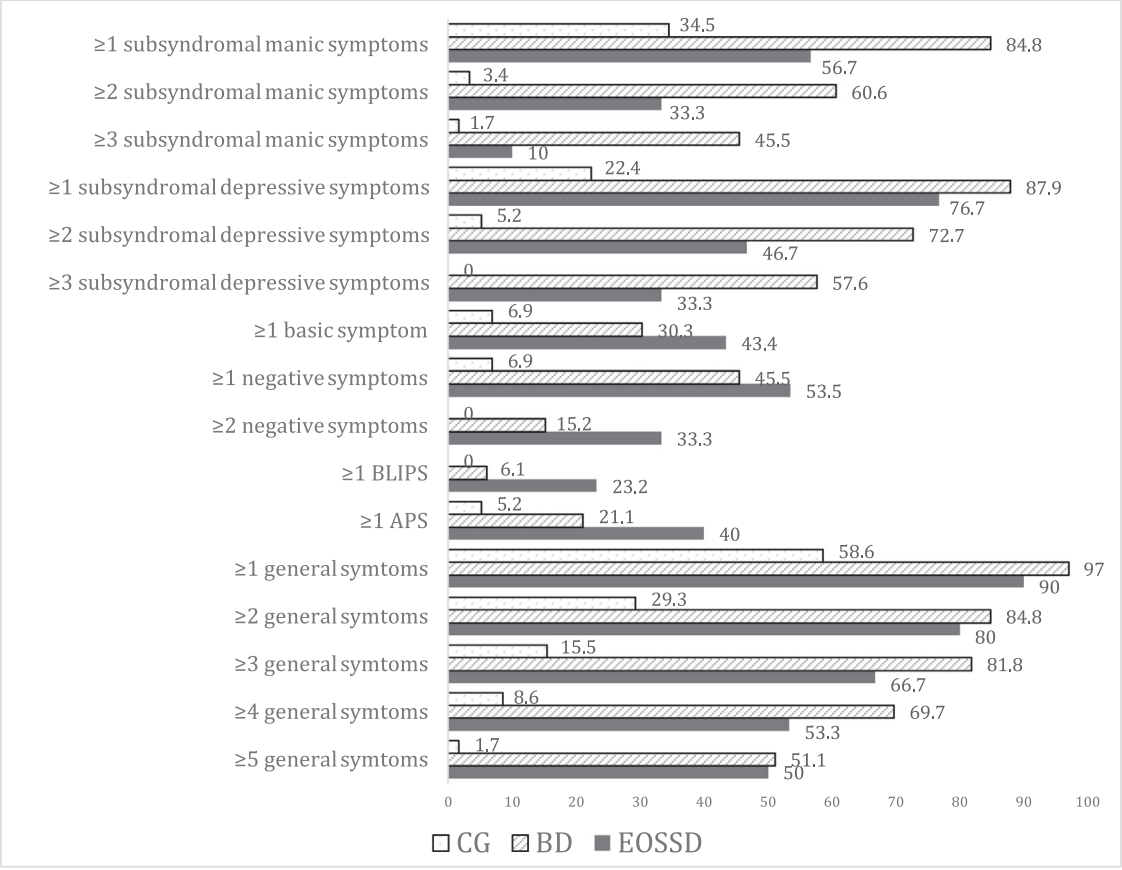

Fig. 2. Comparison of the groups (EOSSD, BD, CG) in terms of symptom clusters (%).
EOSSD: Early onset psychosis, BD: Bipolar disorder, CG: Control Group, APS: Attenuated psychotic symptoms, BLIPS: Brief limited intermittent psychotic symptoms.

Table 4
Logistic regression analysis for distinguishing prodromal stage of BD from EOSSD.

	Wald	df	*p* value
BLIPS	3.195	1	0.074
≥2 negative symptoms	0.001	1	0.972
≥1 basic symptoms	0.000	1	0.993
≥1 APS	0.000	1	0.992
≥3 subsyndromal depressive symptoms	0.020	1	0.888
≥3 subsyndromal manic symptoms	5.263	1	0.022*
Comorbidity of ADHD	6.935	1	0.008*

Binary logistic regression analysis.
* $p < 0.05$, BLIPS: brief limited intermittent psychotic symptoms, APS: attenuated psychotic symptoms, ADHD: attention deficit and hyperactivity disorder.

Description of Table 4: The results of logistic regression analysis that was employed to estimate which prodromal symptom clusters were more predictive for distinguishing prodromal stage of BD from EOSSD are demonstrated.

stage enhanced the risk for BD. In addition, the presence of BLIPS ($p = 0.074$) increased the tendency toward risk of EOSSD (Table 4).

3.6. Latent class analysis

A total of 121 adolescents (BD, EOSSD, and CG) were assigned to four different subgroups by means of latent class analysis according to prodromal symptom clusters (log likelihood = –521.4509, BIC = –1282.691). The size of each class (1, 2, 3, and 4) was calculated as follows: 26, 37, 16, and 42. The individuals in Class 1 were presented with nonspecific symptoms, Class 2 included individuals with predominantly mood and nonspecific symptoms, Class 3 was characterized by predominantly psychotic and nonspecific symptoms, and Class 4 was characterized by absence of prodromal symptoms. The characteristics of individuals in each class are given in Table 5.

3.7. Comparison of the prevalence of cluster membership in EOSSD, BD, and CG

The prevalence of membership in the mood and nonspecific symptoms group (Class 2) was significantly higher in BD in comparison with EOSSD and CG ($X^2[2] = 37.577$, $p < 0.001$). On the other hand, the psychotic and nonspecific symptom cluster (Class 3) was significantly higher in the EOSSD group than in other groups ($X^2 = 26.750$, $p < 0.05$). Although the majority of the BD group was clustered in Class 2, the EOSSD group was distributed more evenly. As shown in Fig. 3, 12.1% of BD had psychotic and nonspecific symptoms (Class 3) in the prodromal stage. Furthermore, 20% of the EOSSD group was classified within the mood and nonspecific symptom cluster (Fig. 3). None of the individuals in the CG group was clustered in Class 3.

4. Discussion

In this study, our first aim was to distinguish the prodromal stage of BD and EOSSD during adolescence. The second aim was to investigate the frequency of subgroups that have different trajectories within the prodrome. Our main findings include the following: (1) prodromal symptoms of BD and EOSSD overlapped substantially; (2) ≥3 subsyndromal manic symptoms and ADHD were more specific to the prodrome of BD, and BLIPS were more specific to the prodrome of EOSSD; (3) APS and negative symptoms were not specific to EOSSD during the prodromal stage; and (4) 12.1% of BD was classified within the psychotic symptom cluster, whereas 20% of EOSSD was classified within the mood symptom cluster in prodrome.

Although nearly all of the prodromal symptoms were significantly more prevalent in the prodromal stage of EOSSD and BD than in healthy adolescents, only 8 symptoms were statistically different between the EOSSD and BD groups. Correll et al. (2007) and Olvet et al. (2010) also reported substantially overlapping prodromal symptoms between schizophrenia and BD. However, unlike the findings of Correll et al. (2007), we found that extreme energy, inflated self-esteem, impulsivity, suicidal thoughts, sleeplessness, oppositionality, and temper tantrums were more frequent in the prodrome of BD and suspiciousness was more frequent in the prodrome of EOSSD. Contrary findings may be explained by diverse methodology and the adult samples that were used in the retrospective prodromal studies of schizophrenia by Correll et al. (2007).

Using logistic regression analysis, ≥3 subsyndromal hypo(manic) symptoms and ADHD were more specific to bipolar prodrome, and BLIPS were more likely to be part of the prodrome of EOSSD. In line with our findings, subthreshold hypo(manic) symptoms are the most important predictors for conversion to BD in cohort studies (Vieta et al., 2018). In addition, in studies of patients at high risk for psychosis, BLIPS groups outweighed those reported in the other UHR groups in terms of transition to psychosis (Schmidt et al., 2015; Simon et al., 2011). BLIPS and subsyndromal manic symptoms at the prodromal stage can thus be more crucial in differentiating BD and EOSSD.

On the other hand, it is still controversial as to whether ADHD is a risk factor for BD (Klassen et al., 2010). Youngstrom et al. (2010) suggested that ADHD may lead to increased substance use, greater family conflict, and elevated distress because of impaired peer and academic functioning; these factors can mediate the increased risk for BD. In addition, there have been some findings showing a link between ADHD and BD in the literature. Childhood ADHD was reported to be related to later adolescent BD in prospective studies (Grant et al., 2009; Shur-Fen Gau et al., 2010). In addition, prospective studies of offspring of bipolar patients showed that the children of parents who failed to respond to lithium prophylaxis (lithium nonresponders) manifest neurodevelopmental disorders, including ADHD, learning and motor

Table 5
Characteristics of individuals in prodromal symptom clusters.

	Class 1 (NS)	Class 2 (Mood + NS)	Class 3 (Psychotic + NS)	Class 4 (No symptom)	*Statistics H, X^2, F*	*p value*
N (female%)	26 (57.7)	37 (78.4)	16 (50)	42 (45.2)		
Age (Mean (SD)) (Years)	16.5 (1.5)	16.5 (1.8)	15.7 (1.6)	16 (1.7)	4.320	0.229[a]
Duration of prodromal period (Mean (SD)) (Months)	20.5 (10.5)	28 (8.4)	28.5 (9.1)	5.2 (10.5)	14.348	0.002[a,*]
ADHD comorbidity (*n*%)	2 (7.7)	20 (54.1)	5 (31.3)	1 (2.4)	34.297	<0.001[b,*]
Total score of PAS (Mean (SD))	0.19 (0.1)	0.22 (0.1)	0.27 (0.1)	0.08 (0.08)	13.079	<0.001[c,*]
Psychosis in family (*n*%)	3 (11.5)	8 (21.6)	8 (50)	2 (4.8)	15.600	0.001[b,*]
Bipolar disorder in family (*n*%)	2 (7.7)	9 (24.3)	1 (6.3)	4 (9.5)	4.803	0.168[b]

NS = Nonspecific symptoms.
[a] Kruskal Wallis.
[b] Chi Square.
[c] One way Anova.
* $p < 0.05$.

Description of Table 5: The characteristics of individuals in each subgroup that was determined according to latent class analysis are given.

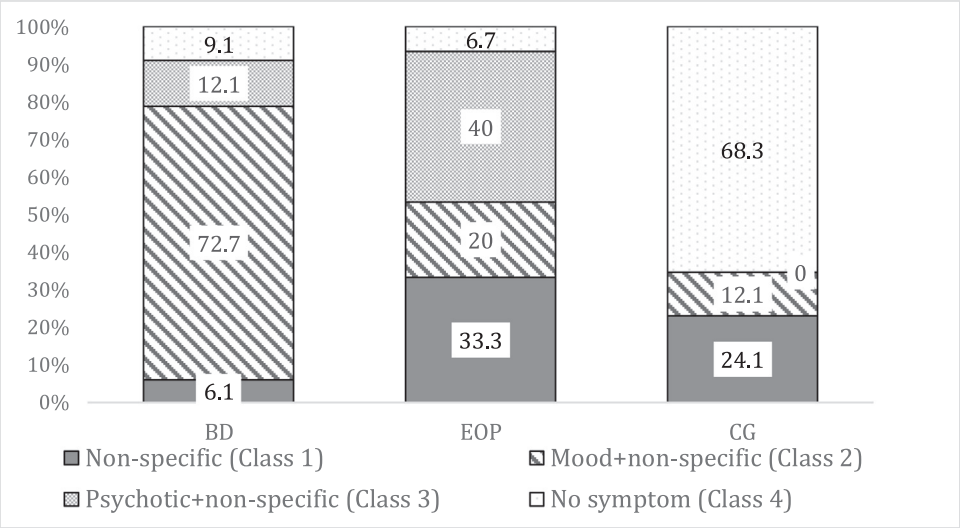

Fig. 3. Comparison of prevalence of cluster membership in each group (%).
BD: Bipolar disorder, EOSSD: Early onset schizophrenia spectrum disorder, CG: Control group.

disabilities, along with problems in cognition, emotional regulation, and socialization (Duffy, 2014). Consequently, although ADHD and BD have some shared risk factors and neurocognitive dysfunctions (Joseph et al., 2008; Klassen et al., 2010), the causal relationship between ADHD and BD is still speculative (Youngstrom et al., 2010).

We also found that the onset pattern and the symptoms of prodromal stage of psychotic and nonpsychotic BD were quite similar, except for a significantly higher prevalence of ≥3 subsyndromal manic symptoms in nonpsychotic BD. This result is in line with previous work (Correll et al., 2007). It also supports our finding of substantial prodromal overlap between EOSSD and BD and the importance of manic symptoms for distinguishing between these disorders in the prodromal stage.

Even though basic symptoms, APS, and negative symptoms were at least 1.3 times higher in EOSSD than BD, they were insufficient to distinguish these disorders at the prodromal stage. In line with this finding, Duffy (2014) suggested that offspring of bipolar patients (lithium nonresponders) demonstrate negative symptoms and APS during the prodrome, and the end-stage disorder of these individuals can be both mood and psychotic spectrum illnesses. To our knowledge, no studies have directly compared BD with EOSSD in terms of prodromal symptom clusters. However, LoCascio et al. (2016) and Fux et al. (2012) compared UHR and/or early-onset psychosis groups with clinical controls that consisted of different psychiatric disorders by using the structured interview for prodromal syndromes (SIPS) and schizophrenia proneness instruments, child and youth version (SPI-CY). They found that compared with clinical control, patients with early-onset psychosis/UHR had significantly more frequent and severe positive, negative, disorganization, and basic symptoms. Some factors may explain our results regarding APS, basic symptoms, and negative symptoms. First, since Fux et al. (2012) and LoCascio et al. (2016) did not use only BD as a CG, these prodromal symptom clusters can be higher in BD. Second, an inadequate sample size in the patient groups may have also caused this result. Last but not least, because negative symptoms tend to be more frequent in male schizophrenia patients than in females, female predominance in EOSSD could have diminished the effect of negative symptoms in distinguishing BD and EOSSD at the prodrome (Canuso and Pandina, 2007).

Premorbid adjustment of EOSSD and BD was similar in our study. In contrast to our findings, McClellan et al. (2003) reported higher rates of premorbid social withdrawal and global impairment in adolescents with schizophrenia than in adolescents with BD and psychosis not otherwise specified. Our finding of similar premorbid adjustment between EOSSD and BD might be explained by the exclusion of patients with mental retardation that was more prevalent in EOSSD and the higher comorbidity rate of ADHD in BD. Furthermore, compared with females, male patients with schizophrenia have a higher prevalence of premorbid social adjustment problems (Nicolson and et. al., 2000; Röpcke and Eggers, 2005). Therefore, female dominance in the EOSSD might also have caused better premorbid adjustment scores in this group.

Importantly, during the prodromal stage, 12.1% of those with BD were grouped into a psychotic and nonspecific symptom class; 20% of those with EOSSD were grouped into a mood and nonspecific symptom class. These subgroups are supportive of presentations that have the potential to converge into differently formed phenotypes (Vieta et al., 2018). This outcome is in accordance with studies stating that progression to BD occurred in 15.3% to 25% of those patients with psychosis (Correll et al., 2008; Werry et al., 1991). In addition, Alloy et al. (2012) reported that psychosis emerged in 11% of individuals at risk for BD within 4.5 years of follow-up. Since our patients were assessed during adolescence, their diagnosis can still change in adulthood. Thus, we have been following up our patients both to detect the endpoint of their disorders and to investigate which factors can guide us to predict their course.

Although the retrospective cross-sectional design of this design might cause recall bias, this is the first study in which individuals with BD and EOSSD were compared directly in terms of prodromal symptom clusters. One limitation of our study was that the CG could not have been matched with patient groups in terms of gender and other sociodemographic features because of systemic randomization. Moreover, the limited sample size, which was caused by the rarity of EOSSD and BD during adolescence, was a disadvantage of the current study. Thus, the findings cannot be generalized. However, from the comparison of those limited number of adolescents in the EOSSD and BD groups, we could detect which prodromal symptom clusters were more specific for each disorders. Our other strength was the diagnostic verification of patients throughout three steps (K-SADS-PL, assessment of T.B., and reevaluation by jury).

5. Conclusion

The prodromal stages of BD and EOSSD were quite similar. Subsyndromal manic symptoms and ADHD were more specific to the prodrome of BD, and BLIPS was more specific to the prodrome of EOSSD. Surprisingly, negative symptoms, basic symptoms, and APS

were not specifically part of the prodrome of EOSSD. In addition, 12.1% of BD was in the psychotic symptom cluster; and 20% of EOSSD was in the mood symptom cluster during the prodromal stage. Our findings suggest that subsyndromal manic symptoms, ADHD, and BLIPS may be a guide in distinguishing the prodromal stage of EOSSD and BD during adolescence. A prospective longitudinal study needs to be designed to ascertain if these prodromal symptom clusters are enough to predict the clinical identification of adolescents at risk for EOSSD and BD. Given the overlapping symptoms of the prodromal stage, a prospective study should combine symptom clusters with biomarkers, including neurocognitive tests and neuroimaging, to enhance prediction power.

Disclosure of potential conflicts of interest

None.

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Informed consent

Informed consent was obtained from all individual participants included in the study.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ege University Clinical Researches Ethical Committee (16-11.1/12) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.03.051.

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