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Abstract

Background

Children with autism spectrum disorder (ASD) have varied comorbidities. With regard to comorbidity, there has been increasing interest in bipolar disorder (BP) in children. However, the prevalence of BP with ASD has varied because of the methodological differences used. Therefore the adequate criteria for determining BP in children are still debated. The purpose of this study is to identify reliable prevalence of BP and to evaluate a variety of subclinical BP symptoms in children with ASD.

Methods

This is a cross-sectional and case-control study. The participants were 110 referred children aged 6-15 years: 46 with ASD (the case group), 64 without ASD (the control group). We used the strict operational criteria for diagnosing BP, and assessed the presence of subclinical BP symptoms using a semi-structured diagnostic interview.

Results

None of the children were diagnosed with BP in the case group, although two children were diagnosed with BP in the control group. Based on the subclinical BP symptoms, the prevalence of elation/expansive mood and racing thoughts was significantly higher in the case group than in the control group: 26.1% versus 3.1% ($p<0.001$) and 32.6% versus 9.4% ($p=0.002$), respectively.

Conclusions

Our finding indicates that school-aged ASD children frequently present subclinical BP symptoms. It is important to be aware of over-diagnosis of BP, even though the children present subclinical BP symptoms, and to provide the children with effective treatments.

Key Words: Autism spectrum disorder; Bipolar disorder; Children; Comorbidity

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder that is characterized by certain

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core features, such as deficient social interaction, impaired communication, and repetitive and stereotyped patterns of behavior, interest, and activities[1]. Children with ASD have varied symptoms, such as frequent mood dysregulation or exhibition of anxiety[2-5]. Some of the symptoms have recently been the focus of research because these symptoms meet certain criteria for comorbidity, such as anxiety and depression[2-6]. With regard to comorbidity, there has been increasing interest in bipolar disorder (BP) in children and adolescents, and the adequate criteria for BP in children are still debated[7-11]. The essential feature of BP is recurrent mood episodes in terms of symptomatology, a clinical course that is characterized by the occurrence of one or more manic episodes and also one or more major depressive episodes[1]. The manic symptoms, such as elation/expansive mood, increased goal-directed activity and racing thoughts, should be intensive and cannot be stopped voluntarily. Additionally, these symptoms need to last some days to qualify for a diagnosis of BP[1]. Traditionally BP has been thought to be rare in children[10,12,13], and irritable mood and elation are a matter of controversy, because these symptoms do not necessarily fulfill the criteria for BP diagnosis. The Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-Ⅳ-TR)[1] incorporates the concept of wide-open criteria which does not need to fully satisfy the strict criteria for BP; consequently, the interpretation of criteria of being BP has expanded since the 1990s[12]. Taking this viewpoint, many studies indicated that children with these symptoms should be given a diagnosis of wide-open criteria[14]. However, in the past two decades, there has been increasing interest in the idea that children with BP that clinically resembles BP in adults may be much more common than previously recognized[10,12]. Conversely, other studies warn against the possibility of over-diagnosis of BP in children[14-16]. Therefore, there has been no clear consensus on the prevalence of BP with ASD, owing to differences in the diagnostic criteria and the diagnostic approach for subjects in each study. Furthermore, the ages or intellectual levels of the participants were not the same in those studies[8,9,11,17-20].

The purpose of this study is to identify reliable prevalence and types of BP in children with ASD. To avoid the confusion in evaluation of symptoms, we used the strict criteria of BP, and excluded children with mental retardation. In addition, we evaluated a variety of subclinical symptoms of BP in children with ASD that does not fulfill the strict criteria of diagnosis, such as insufficient length of time of symptoms, or comparatively moderate/less intensity of symptoms.

Methods

Design

This is a case-control study of the prevalence of BP in children with ASD (the case group) and children with other mental disorders (the control group).

Participants

The subjects were elementary or junior high school students, ranging in age from 6 to 15 years, who were consecutively referred for the first time to the children's psychiatry outpatient clinic of Osaka City University Hospital between July 2007 and September 2010, and were followed up for at least 3 months to provide a psychiatric evaluation. The diagnostic approach for ASD was based on the following three sources: 1) a comprehensive developmental history; 2) the clinician's interview with each child and their parents; and 3) direct observations of the children. A diagnosis of ASD was made using the criteria in DSM-Ⅳ-TR.

Initially 137 children consented to participate in the study. In order to investigate subjective

psychophysical impairments, we excluded children with mental retardation (IQ <70 on the Wechsler Intelligence Scale for Children, Third Edition [WISC-Ⅲ])[21] (n=22), and intractable epilepsy (n=1) from our study. There were four consent denials. The remaining children (n=110) were divided into two groups: 46 children with ASD (the case group) and 64 children without ASD (the control group). The WISC-Ⅲ was used to evaluate the intelligence of all subjects in the case group. For the control group, assessment of intelligence was based on information given by parents and teachers, and direct observations. None of the subjects had a history of drug abuse or organic brain syndrome.

We explained the investigational purpose, procedures, potential risks, and alternatives to participation, and obtained written informed consent from the participants and their parents. The study protocol was reviewed and approved by the Human Subject Review Committee of Osaka City University.

Procedure and Instruments

BP diagnoses were confirmed by experienced child psychiatrists based on DSM-Ⅳ-TR criteria, the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime-Japanese version (K-SADS-PL-J)[22,23], a comprehensive developmental history, a clinician's interview with the children and parent (s), and direct observations of the child. We also used the K-SADS-PL-J in order to evaluate the detailed subclinical symptoms for BP of the participants[24]. The K-SADS-PL-J is a semi-structured diagnostic interview designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-Ⅳ-TR criteria, and administered by interviewing a parent and the child. In this study, we took into consideration that most children with ASD have difficulty in describing their symptoms by themselves, so there was concern about the reliability and the validity of the information from these children. We used the K-SADS-PL-J only for the parent of the subjects. The K-SADS-PL provides four screen interview items to assess manic symptoms: elation/expansive mood, decreased need for sleep, increased goal-directed activity, and racing thoughts. Of the four symptoms, "decreased need for sleep" is not specific to BP and can occur in other mental disorders. Therefore, focusing on subclinical manic symptoms, in this study, we chose three screen items: elation/expansive mood, increased goal-directed activity, and racing thoughts. The screen items are organized for one question to evaluate one answer in three levels: not present, subthreshold, and threshold. The threshold score for elation/expansive mood requires the following: "Mood and outlook are clearly out of proportion to circumstances; noticeable to others and perceived as odd or exaggerated. Experiences elevated mood daily, or almost daily, at least 50% of time awake for at least four days–or for briefer periods of time repeatedly[22]." The subthreshold score for the same item reflects the following symptoms: "Definitely elevated mood and optimistic outlook that is somewhat out of proportion to the circumstances. Mood occurs at least three times a week and persists for more than 3 hours each time." For increased goal-directed activity, the threshold score requires: "Moderate to severe increase in general activity level involving several areas, or marked increase in one or more areas. Activity involvement is excessive, more than what would be expected by a typical child his/her age." The subthreshold score for the second item needs: "Mild but definite increase in general activity level involving several areas." The threshold score for racing thoughts requires: "Racing thoughts cause significant distress or impairment. Thoughts cannot be stopped voluntarily." The subthreshold score for the third item is: "Racing thoughts cause minor distress or impairment." The threshold score indicates significant distress or impaired state, and the subthreshold score reflects minor distress or impaired state. We adopted the subthreshold criteria as

the definition of subclinical manic symptoms.

Analysis

All statistical analyses were performed using SPSS version 22.0 statistical software (SPSS Japan Inc., Tokyo, Japan). The chi-squared test was used for categorical comparisons of the data. For continuous variables, the Mann-Whitney U-test was employed because data were not normally distributed. A probability (p) value of <0.05 was considered statistically significant, and all statistical tests were two-tailed.

Results

Demographic characteristics of all the participants are shown in Table 1. Forty-six children were in the case group, comprising 35 males (76.1%). The mean of full IQ scores on the WISC-Ⅲ was 95.6. Sixty-four children were in the control group, comprising 22 males (34.4%). There was a statistical difference in age ($p=0.004$) between the two groups. The case group had a significantly higher proportion of male subjects than the control group ($p=0.000$). The number of participants receiving public assistance or having a single parent was not significantly different across groups.

In the control group, the most frequently diagnosed disorder was anxiety disorder (n=28), followed by depressive disorder (n=16), eating disorder (n=9), adjustment disorder (n=7), trichotillomania (n=5), attention deficit hyperactivity disorder (n=2), conduct disorder (n=3), and BP (n=2). Some controls had comorbid diagnoses. Two children were diagnosed with BP in the control group but none were in the case group.

Table 2 shows the comparison between the case group and control group of the rate of subclinical manic symptoms. The data show the number of children who met the three screen items for mania: elation/expansive mood, increased goal-directed activity, and racing thoughts. A statistically significant difference was found elation/expansive mood ($p=0.000$) and racing thoughts ($p=0.002$). The details of the results of the number of children that fulfil the evaluation of threshold, subthreshold, or not present for manic symptoms in three screen items were as follows. In the item of elation/expansive mood, the number of children in the case group was 0 (0.0%), 12 (26.1%) and 34 (73.9%), and in the control group 2 (3.1%), 2 (3.1%) and 60 (93.8%), respectively. In the item of increased goal-directed activity, the number of children in the case group was 0 (0.0%), 8 (17.4%) and 38 (82.6%), and in the control group 2 (3.1%), 12 (18.8%) and 50 (78.1%), respectively. In the item of racing thoughts, the number of children in the case group was 0 (0.0%), 15 (32.6%) and 31 (67.4%), and in the control group 2 (3.1%), 6 (9.4%) and 56 (87.5%), respectively.

Discussion

In this study, we elucidate the absence of diagnosed with BP in school-aged children with ASD, but many of those children present subclinical manic symptoms, such as elation/expansive mood and racing thoughts.

In previous study, the prevalence of BP in children was also very low, 0.1%-0.7% in community samples[25-27]. Some studies, including the one by Mattila[2,4], reported that none of the children were diagnosed with BP in ASD samples. In our study, using the traditional strict criteria, none of the children were diagnosed with BP in the case group. The total prevalence of BP in our study was 1.8% (2/110 participants), consistent with a meta-analysis by Van Meter indicating 1.8% (95% CI; 1.1%-3.0%)[28]. Generally, the BP prevalence for adults is higher than for children[29,30]; nevertheless, some

Table 1. Participants Characteristics

Characteristics	Subgroups		Analysis	
	ASD (n=46)	non-ASD (n=64)	χ^2/U	p
Age in years[a]	11.4 (2.5)	12.6 (2.3)	1003.00 [c]	0.004*
Males[b]	35 (76.1%)	22 (34.4%)	18.65 [d]	0.000*
Public assistance[b]	4 (8.7%)	6 (9.4%)	0.02 [d]	0.903
Absence of father or mother[b]	13 (28.3%)	23 (35.9%)	0.72 [d]	0.397

[a] Values are expressed as mean (SD) and [b]values are expressed as n (%). [c] Mann-Whitney U-test. [d] Chi-squared test. *p<0.05. ASD, autism spectrum disorder.

Table 2. Subclinical Manic Symptoms

	Subgroups		Analysis	
Screen Items	ASD (n=46)	non-ASD (n=64)	χ^2	p
Elation/expansive mood[a]	12 (26.1%)	2 (3.1%)	12.70	0.000*
Increased goal-directed activity[a]	8 (17.4%)	12 (18.8%)	0.33	0.855
Racing thoughts[a]	15 (32.6%)	6 (9.4%)	9.35	0.002*

[a] values are expressed as n (%). *p<0.05. ASD, autism spectrum disorder.

previous studies indicated that the prevalence of BP is only around 1% to 5% in adults[28,31,32]. However, some studies reported a high prevalence of BP in children with ASD: 21.0%-27.3%[8,30,33]. Furthermore, the studies that reported a high prevalence of BP in children with a neurodevelopmental disorders, including ASD, employed "broadband criteria" of BP[7-9,17-20,33-35]. For assessment of criteria of BP, some of those studies adopted telephone surveys[36] or ignored the period of time that symptoms continued[7-9,17-20], in addition to there being differences in ages[8,9,33], intellectual levels of subjects, or the diagnostic approach of the studies[7,9,17,18,33-35]. One reason for such contradicting results is that BP diagnostic criteria are too flexible, and BP symptoms, especially those of children, are convoluted and incomprehensible[12].

The criteria for BP diagnosis has changed with the times. The main feature of BP is recurrent mood episodes: manic and depressive phases. A clinically manic phase is more marked in BP criteria. Since the 1980s, according to the DSM-Ⅲ[37], euphoric mood, hyperactive behavior, and fright of ideas are diagnosed as the core features of the manic phase of BP. Since the 1990s, in DSM-Ⅳ-TR, for satisfying the criteria for BP, those symptoms are required to fulfill some duration: at least one week, or four days. After the DSM-Ⅳ-TR was published, the concept of wide-open criteria, which does not need to fully satisfy the strict criteria as above for BP, was advocated. In addition, the criteria for BP in children and adolescent onset cases was defined in various ways in each study, such as "non-classical" criteria[8,18,33]. As a consequence, the number of BP cases in children has greatly increased. In this study, when we focused on the results using the subthreshold criteria to evaluate their symptoms in the K-SADS-PL, elation/expansive mood and racing thoughts, the difference between the case and the control group was clearly evident. This result shows that many children with ASD present with manic symptoms when we examine them based only on mild subclinical symptoms. Our findings can explain the reason for the high prevalence of BP in children with ASD in other studies, as they evaluated children with symptoms that were less severe or of shorter duration.

Furthermore, the incomprehensibility of the manic symptoms in children makes this argument more complicated[10]. First is the overlap of the symptoms for diagnoses; irritability and elation/expansive mood are included in the criteria for not only BP but also many other disorders, such as major depressive disorder and anxiety disorder[1,10]. Even in adults, the diagnosis of BP needs to be carefully distinguished from depression, and clinicians need to determine whether manic or hypomanic symptoms exist by collecting as much information about the patient's medical history as possible[1]. Second, especially with regard to children, it is quite difficult to explain their symptoms adequately[38]. Many studies evaluated results based on interviews with their parents, as we did[6,8,9,13]. It is still difficult to know children's symptoms precisely because their symptoms fluctuate depending on the relationship between their parents.

Our findings should be considered in the context of some methodological limitations. The participants did not involve a normal control group and were recruited from only one child psychiatric clinic of a university hospital, and the sample size was relatively small. Therefore our findings might not be generalized to community samples. There are significant differences in the average age and sex ratio between the case group and the control group. However, the onset of BP usually occurs in adulthood[31,39] and in both sexes equally[40,41], so that the differences in age for only one year and sex ratio between the two groups did not affect our results. Furthermore, the WISC test was not used in all individuals in the control group, but for members suspected of mental retardation, we performed it for assessment. In addition, owing to the cross-sectional design of this study, a longitudinal course of manic symptoms could not be established from these data, which is important in order to make a definitive diagnosis of BP. Larger and longitudinal multi-centered studies are necessary for a better understanding of manic symptoms in ASD children.

In conclusion, we found the prevalence of patients having comorbid BP was low among children with ASD when experienced child psychiatrists diagnosed them using the traditional strict criteria for BP. However, many children with ASD presented with subclinical manic symptoms when they were diagnosed using only symptoms that do not sufficiently meet the criteria. Our findings imply the spread of an over-diagnosis of BP. In daily practice, psychiatrists should avoid not only easily diagnosing children as BP but also prescribing medication, even though the children have subclinical symptoms of BP.

Authors' contributions

DM planned the study. YO and DM redesigned the study. YO was the principal investigator of this study. YO, DM, and HR collected and analyzed data and wrote the first draft of the paper. NA, YI, EY, NA, EK, and HT collected and interpreted data. KI supervised the study. All authors contributed to and have approved the final manuscript.

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