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YUSUKE MIKI, DAI MIYAWAKI, AYAKO GOTO et al. Disruptive Mood Dysregulation Disorder in Children with Autism Spectrum Disorder. *Osaka City Medical Journal*. 2020, 66, 1-11.

Osaka City Med. J. Vol. 66, 1-11, 2020

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Abstract

Background

Irritability is one of the most important reasons for which children get referred to child mental health services. Disruptive mood dysregulation disorder (DMDD) is a diagnostic category characterized by severe and chronic irritability in children, and is associated with long-term adverse outcomes. However, little is known about DMDD in autism spectrum disorder (ASD). The aim of this study was to assess the prevalence of DMDD and the association between DMDD and comorbid psychiatric disorders in children with ASD.

Methods

Study participants consisted of 87 children with ASD aged 6-18 years, who were referred to a child psychiatry outpatient clinic at Osaka City University Hospital. A diagnosis of DMDD and associated symptoms were assessed through a semi-structured interview and the Child Behavior Checklist (CBCL).

Results

Of all study participants, approximately 17% (n=15) had a diagnosis of DMDD, although 60% (n=52) showed symptoms of DMDD. The total, internalizing and externalizing CBCL scores, as well as 6 of the 8 subscales (Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, Aggressive Behavior), were significantly higher in children with DMDD than in children without DMDD.

Conclusions

Not assessing the frequency or duration of the symptomatic irritability is likely to increase the risk of over-diagnosing DMDD. Children with ASD and DMDD had more severe psychopathological symptoms than children with ASD without DMDD. Identifying DMDD in children with ASD may be helpful to the assessment of comorbid internalized/externalized symptoms as well as to the selection of appropriate therapeutic interventions, including pharmacotherapy.

Received August 27, 2019; accepted October 8, 2019.
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Key Words: Disruptive mood dysregulation disorder; Autism spectrum disorder; Depression; Anxiety disorder; Irritability

Introduction

Irritability is a common symptom in children and is one of the most common reasons for which children are referred to child and adolescent mental health services[1]. In a community sample, approximately 28%-51% of children aged 9-16 years experienced irritability-related symptoms[2]. Chronic and severe irritability is the cardinal symptom of Disruptive mood dysregulation disorder (DMDD), having newly appeared in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)[3]. DMDD is associated with long-term poor and adverse outcomes[1].

DMDD is characterized by (a) severe recurrent temper outbursts that are grossly out of proportion in intensity or duration to the situation (on average three or more times a week), (b) persistent irritable/angry mood between temper outbursts throughout most of the day, nearly every day. In order to meet diagnostic criteria, these symptoms must be seen in at least two of three settings (at home, at school, with peers), and be present for at least 12 months. Additionally, DMDD cannot be first diagnosed prior to the age of 6-years-old or after the age of 18-years old, and should have an onset prior to the age of 10-years-old. Finally, DMDD cannot be diagnosed if the child has already been diagnosed with bipolar disorder (or any manic or hypomanic episode)[3].

In the 1990s, children with severe non-episodic, chronic irritability were considered to have pediatric bipolar disorder without significant manic episodes. However, some researchers were concerned about over-diagnosing children and using excessive medication to treat bipolar disorder. Longitudinal studies have suggested that such children showed a higher risk of having depression and anxiety in the future, rather than having bipolar disorder[4,5]. With respect to the prevalence of DMDD symptoms, which consist of temper outbursts and irritable mood, Dougherty et al report that 8% of 6-year-old children from a community sample have DMDD symptoms[6], while 26% of 6-12-year-old children from a clinical sample showed both symptoms for 6 months in at least 2 settings[7]. It must be noted that these reports used other assessment scales for psychiatric disorders for oppositional-defiant disorder (ODD), prior to the establishment of a DMDD diagnosis in the DSM-5 which could then frame the assessment of DMDD symptoms. Therefore, researchers have pointed out that these studies are limited in that they used arbitrarily chosen thresholds, without strictly applying the duration and frequency criteria of the symptoms as per the criteria set forth by the DSM-5 for the diagnosis of DMDD.

Irritability is also common in children with autism spectrum disorder (ASD), which is characterized by persistent deficits in social communication/interaction and restricted, repetitive patterns of behavior, interests, or activities, as described in the DSM-5[3]. Irritability presents as severe temper tantrums or over reactivity[8]. Maladaptive emotional responses in youth with ASD have a variety of phenotypes, including but not limited to irritability, poor anger control, temper tantrums, self-injurious behavior, and aggression[9,10]. These maladaptive emotional responses are directly associated with core features of ASD[11]. According to the DSM-5, children with ASD frequently present with temper outbursts only when, for example, their routines are disturbed. In such an example, the temper outbursts would be considered secondary to the ASD, and the child should not receive a diagnosis of DMDD[3]. However, with regards to whether children with ASD have comorbid DMDD or not, there are no studies strictly assessing or excluding the diagnosis of DMDD

which take into account the severity of the temper outbursts and irritable mood. The prevalence of DMDD in youth with ASD, and the association between a DMDD diagnosis and symptoms and other psychiatric comorbidities in youth with ASD, remain unknown. Therefore, the aims of this study are 1) to examine the prevalence of DMDD diagnoses and symptoms in children with ASD in a clinical sample, applying rigorous criteria based on the DSM-5, and 2) to examine the association between the diagnosis of DMDD and other psychiatric disorders (i.e. depression, anxiety) in children with ASD in a clinical sample.

Methods

Participants consisted of 94 children with ASD aged 6 to 18-years-old who had been referred to the child psychiatry outpatient unit in Osaka City University Hospital between April 2018 and December 2018. We excluded children with intellectual disability (n=5) who had difficulties in evaluating symptoms, as well as children with bipolar disorder (n=2), as assessed according to the DSM-5 diagnostic criteria. As a result, a total of 87 cases were retained for the study. We explained to participants and their parents the purpose of the study, as well as its procedures, potential risks, and alternatives to participation, and we obtained written informed consent from all children and their parents. The Human Subject Review Committee of Osaka City University reviewed and approved of the study protocol.

The diagnosis of ASD was based on the following sources: 1) a comprehensive developmental history from the parents, 2) an interview of both the child and their parents conducted by the clinician, 3) direct observations of the subject by the two child psychiatrists. Finally, a diagnosis of ASD was delivered according to the criteria of the DSM-5. To diagnose comorbid psychiatric disorders, we used the Japanese version of the Kiddie Schedule for Affective Disorder and Schizophrenia Present and Lifetime version (K-SADS-PL-J)[12]. This consists of a semi-structured interview designed to assess any current and past episodes of psychiatric disorders in children and adolescents according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text-revision (DSM-Ⅳ-TR) criteria and is administrated through interviews with the child and their parents. This diagnostic interview has good inter-rater reliability and concurrent validity[13]. After the diagnostic interview was completed, a multidisciplinary team meeting was held to decide on the most appropriate diagnosis for all participants.

Although ODD cannot co-exist with DMDD according to the DSM-5[3], because comorbidity of DMDD was of interest in this study, this exclusion was not applied here. Additionally, we collected information, from interviews, on 1) whether a child only had one parent (absence of father or mother), 2) family income, and 3) years of education of the parents. With regards to family income, we categorized households with public assistance or with an annual income of less than three million yen as “low-income”.

Assessment of DMDD diagnosis and DMDD symptoms

As previously mentioned, there are no diagnostic interview tools specifically designed for the diagnosis of DMDD that take into account the exact duration and frequency criteria in the DSM-5. Therefore, in this study, we created a new semi-structured interview, based on the DSM-5, to conduct with children’s parents. The content of the interview was based on the criteria of the DSM-5, and each item asked the following: 1) Does your child often have temper outbursts? How many times a week on average does your child have temper outbursts? When did the symptoms start? How long

does your child had the symptoms? 2) Does your child usually get irritable or angry? Does the irritable mood persist throughout most of the day? When did the symptoms start? How long has your child had the symptoms? 3) In how many situations are the symptoms present? Are the symptoms present at home, at school, with peers? On obtaining answers to these questions from the interviews with parents, we delivered a diagnosis of DMDD when 1) temper outbursts occurred 3 or more times per week and, at the same time, irritable mood lasted most of the day, 2) these symptoms had persisted for more than 12 months, 3) these symptoms were present in at least two of three settings (at home, at school, with peers), and 4) age at onset met the criteria set forth by the DSM-5. By assessing these symptoms, we investigated whether symptoms (temper outbursts and irritable mood) were of diagnostic severity or subthreshold (below the level warranted for a diagnosis of DMDD). For example, if the child had temper outbursts at least 3 times a week, we categorized these as "temper outbursts as symptoms of DMDD", and, if not, we categorized them as "subthreshold temper outbursts". Additionally, we examined the test-retest reliability and inter-rater reliability of this interview, re-obtaining participant answers again at a later date. The test-retest reliability was kappa=0.832 (n=23), with a 46-day interval on average, and the inter-rater reliability was 0.806 (n=13), with a 63-day interval on average. Both of the reliability rates were considered to confirm the validity of the interview.

Child Behavior Checklist (CBCL)

For the evaluation of holistic psychopathologies, we used the standardized Japanese version of Child Behavior Checklist (CBCL)[14]. CBCL is a parent-report rating scale of child psychopathology consisting of 113 questions developed by Achenbach and Dumenci[15]. Each question has the following response scale: 0=not true (as far as you know), 1=somewhat or sometimes true, 2=very often or often true. The scales consist of three domains (total score, internalizing score, externalizing score) and eight subscales (Withdrawal, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, Aggressive Behavior).

Statistical Analysis

All statistical analysis was performed using SPSS version 25.0 statistical software (SPSS Japan, Inc., Tokyo, Japan). Descriptive data were presented as means, standard deviations (SD), medians, and ranges. A chi-square test or Fisher's exact test was used to compare categorical variables, as appropriate. A Mann-Whitney's U-test or Student's t-test was used to compare continuous valuables, whether the data was normally distributed or not. P-values$<$0.05 (using a two-sided probability) were considered to reflect statistical significance.

Results

Of all the participants (n=87), the mean age of the sample was 12.5-years-old (ranging from 6 to 17-years-old, SD 2.8), and 55.2% (n=48) of the sample was male. 21.8% (n=19) of the sample was from a low-income household, 25.3% (n=22) only had one parent (absence of father or mother). Parents' education had a mean duration of 13.9 years (ranging from 9-16 years, SD 1.6). The prevalence of comorbidities was 44.8% (n=39) for generalized anxiety disorder, 43.7% (n=38) for ODD, 39.1% (n=34) for attention-deficit hyperactivity disorder (ADHD), 32.2% (n=28) for social anxiety disorder, 19.5% (n=17) for major depressive disorder, 13.8% (n=12) for obsessive-compulsive disorder, 12.6% (n=11) for chronic tic disorder, 9.2% (n=8) for conduct disorder (CD), 8.0% (n=7) for adjustment disorder, 6.9% (n=6) for dysthymia, 6.9% (n=6) for Tourette disorder, 5.7% (n=5) for

Table 1. Prevalence of DMDD symptoms and diagnoses in children with ASD

	N=87	Symptoms present in at least 2 settings
Symptoms [(n (%)]		
temper outbursts	60 (69.0)	35 (40.2)
temper outbursts less than 3 times a week	25 (28.7)	
temper outbursts 3 or more times a week (DMDD symptoms)	35 (40.2)	
irritable mood	64 (73.6)	33 (37.9)
irritable mood present but less than most of the day	36 (41.4)	
irritable mood present most of the day (DMDD symptoms)	28 (32.2)	
temper outbursts and irritable mood	52 (59.8)	32 (36.8)
temper outbursts 3 or more times a week and irritable mood present throughout most of the day	23 (26.4)	16 (18.4)
DMDD diagnosis		15 (17.2)

DMDD, Disruptive Mood Dysregulation Disorder; and ASD, Autism Spectrum Disorder.

panic disorder, and 4.6% (n=4) for separate anxiety. Psychotropic agents had already been taken in 18.4% (n=16) of all children. Of these, 10 children had taken antipsychotics, 5 had taken stimulants, 1 had taken benzodiazepines. None of the children had taken antidepressants or a mood stabilizer.

Prevalence rate of DMDD diagnosis and DMDD symptoms

Table 1 shows the prevalence rates of DMDD-related symptoms by severity or by number of situations in which symptoms are present (≧2 or not), as well as the prevalence of DMDD diagnoses in the sample. Of the subjects, 69.0% (n=60) of children with ASD had temper outbursts, while 40.2% (n=35) of the sample showed temper outbursts as a DMDD symptoms (i.e. 3 or more times per week). Of all participants, 73.6% (n=64) of the children with ASD had irritable mood, but 32.2% (n=28) had irritable mood as a DMDD symptoms (i.e. for most of the day). With regards to both temper outbursts and irritable mood, 59.8% (n=52) had both symptoms at the same time, but 26.4% (n=23) had both DMDD symptoms (i.e. temper outbursts three or more times a week and irritable mood throughout for most of the day). Moreover, when considering the number of settings in which symptoms occur, the original 59.8% (n=52) of the children with both symptoms dropped to 36.8% (n=32) of the children with both symptoms present in at least 2 settings. Of the subjects, 26.4% (n=23) with both DMDD symptoms dropped to 18.4% (n=16) with both symptoms present in at least 2 settings. Consequently, 17.2% (n=15) of the subjects strictly met DMDD diagnostic criteria according to the DSM-5, incorporating frequency, duration, and the number of settings in which symptoms occur.

Sociodemographic factors and comorbidities

Table 2 shows the association between sociodemographic data, comorbidities, and DMDD. There were no significant differences between the DMDD and non-DMDD groups in terms of age, sex, family income (low income), or duration in years of parents' education. The rate of absence of a child's father or mother was significantly higher in the DMDD group than in the non-DMDD group [Odds ratio (OR) =6.81, 95% Confidence interval (CI) =2.06-22.49]. On investigating the association between comorbidities and a DMDD diagnosis, there were no significant differences in comorbid depressive or anxiety disorders between the DMDD and non-DMDD groups, while the DMDD group had a significantly higher comorbidity with ADHD (OR=4.00, 95% CI=1.23-13.02), and ODD/CD (OR

Table 2. DMDD and associated sociodemographic factors and comorbidities in children with ASD

	DMDD N=15	Non-DMDD N=72	U/t/χ^2	p	OR (95% CI)
Sociodemographic factors					
age [year: mean (SD)]	11.8 (2.6)	12.6 (2.8)	450.0[c]	0.312	
male [n (%)]	8 (53.3)	32 (44.4)	0.025[b]	0.876	1.09 (0.36-3.34)
Absence of parent [n (%)]	9 (60.0)	13 (18.1)	11.43[b]	0.001*	6.81 (2.06-22.49)
low-income [n (%)]	6 (40.0)	13 (18.1)	3.462[b]	0.063	3.03 (0.92-9.99)
parents education [year: mean (SD)]	14.0 (2.0)	13.8 (1.6)	357.0[c]	0.484	
IQ [score: mean (SD)]	102.6 (13.5)	93.6 (13.4)	1.882[a]	0.067	
Comorbidities					
Mood Disorders	7 (46.7)	20 (27.8)	2.046[b]	0.153	2.28 (0.73-7.10)
Anxiety Disorders	9 (60.0)	47 (68.1)	0.361[b]	0.558	0.70 (0.22-2.22)
ADHD	10 (66.7)	24 (33.3)	5.727[b]	0.021*	4.00 (1.23-13.02)
ODD/CD	14 (93.3)	24 (33.3)	17.96[b]	0.000*	28.0 (3.47-226)

[a]Student t-test; [b] Fisher's exact-test; [c]Mann-Whitney U-test; and * $p<0.05$.

Mood Disorders includes major depressive disorder, dysthymia, adjustment disorder. Anxiety disorders includes panic disorder, social anxiety disorder, separation anxiety, general anxiety disorder, obsessive compulsive disorder, tic disorder, Tourette's disorder. OR, Odds ratio; CI, Confidence interval. DMDD, Disruptive Mood Dysregulation Disorder; ADHD, Attention Deficit/Hyperactivity Disorder; ODD, Opposite Defiant Disorder; and CD, Conduct Disorder.

=28.00, 95% CI=3.47-226) than the non-DMDD group.

CBCL scores and DMDD diagnosis/symptoms

Table 3 shows CBCL scores (total, internalizing, externalizing, and the scores of the eight subscales) of the DMDD and non-DMDD groups. On comparing the two groups, the total scores, internalizing scores, and externalizing scores were significantly higher in the DMDD group than in the non-DMDD group. With regards to the CBCL subscales, 6 of the 8 subscale scores (Anxious/Depressed, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, Aggressive Behavior) were significantly higher in the DMDD group than in the non-DMDD group.

Discussion

Our results suggest two points: First, not assessing the frequency, duration and number of settings in which symptoms are present is likely to increase the risk of over-diagnosing children with ASD and DMDD. Applying strict criteria incorporating these considerations demonstrated that 17.2% of children with ASD in a clinical sample had a concurrent DMDD diagnosis according to DSM-5 criteria. Second, children with ASD and DMDD had a more severe and broader psychopathology than children with ASD without DMDD.

First, our findings suggest that DMDD is likely to become over-diagnosed in children with ASD. In our study, approximately 60% of the children with ASD had temper outbursts and irritable mood. However, the prevalence dropped to less than 50% when taking into consideration frequency criteria (temper outbursts 3 or more times a week and irritable mood throughout for most of the day) set forth by the DSM-5. Moreover, when taking into consideration the duration of the symptoms (symptoms

Table 3. The association of the CBCL scores and DMDD

	DMDD N=15	Non-DMDD N=72	U/t	p
CBCL, mean (SD)				
Total score	75.3 (11.2)	64.7 (8.66)	187.0[b]	0.002*
Internalizing score	75.3 (14.0)	65.4 (9.00)	2.45[a]	0.028*
Externalizing score	69.9 (9.83)	60.4 (11.4)	2.77[a]	0.007*
CBCL subscales				
Withdrawal	72.6 (11.4)	64.1 (8.39)	224.5[b]	0.09
Somatic Complaints	67.5 (11.7)	62.9 (10.4)	319.0[b]	0.183
Anxious/Depressed	74.3 (14.6)	62.8 (8.83)	216.5[b]	0.007*
Social Problems	69.0 (12.4)	61.5 (8.40)	262.5[b]	0.036*
Thought Problems	69.0 (14.0)	60.1 (11.3)	265.0[b]	0.034*
Attention Problems	71.5 (11.5)	61.8 (8.11)	3.63[a]	0.001*
Delinquent Behavior	67.3 (7.32)	59.0 (8.75)	214.0[b]	0.005*
Aggressive Behavior	68.9 (9.71)	60.6 (9.40)	220.0[b]	0.007*

[a]Student t-test; [b] Mann-Whitney U-test; and * $p<0.05$.
CBCL, the Children Behavior Checklist; and DMDD, Disruptive Mood Dysregulation Disorder.

present at least 12 months) and number of settings symptoms are present (at least 2 of 3 settings), the prevalence of rigorously defined DMDD dropped to 17.2% according to the criteria set forth by the DSM-5.

Previous reports have suggested that the prevalence of DMDD is wide-ranging. In a community sample, the 3-month prevalence of DMDD was 0.8%-3.3%[16], 5.3%[17], 8.2%[6], and 9.0%[18]. However, in a clinical sample, the prevalence of DMDD was higher than in the community sample. The 6-month prevalence of DMDD symptoms among 6 to 12-year-old children who had been referred to a child psychiatric outpatient clinic was 26%-31%[7,19]. However, these previous studies failed to use dedicated assessment measure of a DMDD diagnosis, and their diagnoses were performed by evaluating arbitrarily chosen criteria on the frequency or duration of symptoms, rather than the criteria set forth by the DSM-5. For example, most studies used alternative questionnaires or assessment tools for other psychiatric disorders for diagnosing DMDD prior to the development of the DSM-5. For this reason, previous reports often assessed the frequency or duration of DMDD symptoms as 'often or very often', and investigated the '3-month or 6-month' prevalence. Thus, these previous studies had investigated the prevalence of a form of 'proxy-DMDD', rather than true DMDD as defined by the DSM-5. Some researchers have expressed their concern about the validity of a DMDD diagnosis because of the high comorbidity of other psychiatric disorders in addition to its own high prevalence rate[20-22]. However, considering the likelihood of over-diagnosing DMDD in children with ASD as pointed out by our results, the prevalence of DMDD in previous studies may have been artificially inflated as a result of not strictly using criteria set forth by the DSM- 5.

Second, children with ASD and DMDD had significantly more severe psychopathological symptoms linked to depression and anxiety than those without DMDD. Several studies have noted the association between DMDD and other psychiatric disorders. In the 1990s to the mid-2000s, children with severe and chronic irritability had been diagnosed with pediatric bipolar disorder and

received treatment for bipolar disorder, for which there were growing concerns of overdiagnosis and overmedication. These concerns led to the establishment of newly defined criteria in the DSM-5 for the diagnosis of DMDD[3,23] alongside a number of epidemiological and prognostic studies on children with DMDD. As further evidence, a DMDD diagnosis in children means they are predisposed to higher future rates of depression and anxiety or a higher rate of comorbidity of depression and ODD, but not bipolar disorder[6,16]. Few reports had investigated DMDD in children with ASD. Axelson et al reported the prevalence of DMDD in a clinical sample consisting of OCD, CD, ADHD, depression, anxiety disorders, and autism, but the number of children with autism was too small to draw any conclusions about this subgroup[7]. Our study complements a previous study in which children with ASD comorbid with DMDD had more severe psychopathological symptoms characterized by depression and anxiety than children without DMDD.

In addition to symptoms of depression/anxiety, children with ASD and DMDD had a broader range of psychopathological symptoms. The significant prevalence of severe psychopathology linked to Delinquent Behaviors and Aggressive Behaviors from the CBCL subscales in the DMDD group may be explained by the evidence, as noted in previous studies, that DMDD itself often co-exists with ODD/CD characterized by behavioral problems[6,18,21,24]. The significant severe psychopathology linked to attention problems from the CBCL subscales in the DMDD group may also be explained by a previous suggestion that children with ADHD often have comorbid DMDD[25-27]. A previous study had demonstrated that ADHD, ODD, and CD were significantly more common comorbidities in the DMDD group than in the non-DMDD group in a general clinical sample. Our study has further demonstrated that ADHD, ODD, and CD are significantly more common comorbidities in patients with DMDD, even in an ASD clinical sample.

Irritability is a transdiagnostic factor which can be seen in various psychiatric diseases. Despite the difficulty in defining its characteristics, irritability tends to be a focus for treatment by psychotherapy and/or medication. Recent research has pointed to a link between irritability and emotional symptoms in late childhood/early adolescence[28]. Although Malhi et al suggested a preliminary model in which irritability was a symptom leading to the development of internalizing symptoms such as anxiety and depression[29], mechanisms of irritability remain unclear. As suggested in our study, DMDD co-exists with many other psychiatric disorders, specifically with ODD, and DMDD has been incorporated into a new subclassification of ODD in the International Classification of Diseases 11th Revision (ICD-11) as "ODD with chronic irritability/anger"[30]. As such, there remains a nosological debate to this day surrounding the conceptualization of irritability, and whether it is a developmental indicator of internalizing symptoms such as depression and/or anxiety, or a subordinate phenotype of externalizing symptoms such as ODD/CD. Our study clarifies that children with ASD and DMDD have higher scores on internalizing symptoms, such as depression/anxiety, and higher scores on externalizing symptoms, such as Delinquent Behaviors or Aggressive Behaviors, than children with ASD without DMDD. In this study, our results suggest that irritability itself may be an intermediate phenotype between internalizing and externalizing symptoms.

Clinical implications

There is no established management of therapeutic interventions for irritability in children, despite the need thereof in clinical settings. In children with disruptive behavior, research on psychosocial interventions has been limited, especially on parental management training and cognitive behavioral therapy, which have been suggested to be effective[31-33]. With regards to DMDD,

treatment options for children with DMDD are currently limited. A few studies have pointed to the efficacy of psychotherapy in children with DMDD[34,35], and in the case of children with DMDD comorbid with ADHD, a few reports have pointed to the efficacy of pharmacotherapy for the treatment of ADHD symptoms[36-39]. When treating irritability in child psychiatry, clinicians often face difficult decision on whether to treat the irritability directly, the comorbid condition, or both[1]. With regards to children with ASD, some antipsychotics have been approved to treat their irritability. However, due to the broad phenotype of irritability symptoms in ASD, there is no established treatment tailored to the severity and/or characteristics of the irritability. Therefore, treating irritability in children with ASD is often challenging for clinicians because of concerns surrounding the overassessment of symptoms and the overmedication with psychotropics. Although there is no evidence-based therapeutic intervention for DMDD children with ASD at this point, by extrapolation based on the treatment options in previous DMDD studies, our results may support the use of medication to treat severe irritability in children with ASD and DMDD.

Our study suggested that broad psychopathology, including symptoms of depression and anxiety, were more common in ASD children with DMDD than without DMDD. As mentioned above, although irritability is hard to recognize, recognizing DMDD in children with ASD may be helpful for identifying their internalizing and externalizing problems.

Strengths and limitations

A strength of our study was that it investigated the prevalence of DMDD in a clinical sample of children with ASD by performing a semi-structured interview tailored to DMDD. Additionally, though it was already known that DMDD was associated with depression and anxiety, our study enabled us to clarify that ASD children with DMDD had significantly more psychiatric problems, including symptoms of depression and anxiety, than children without ASD.

There were some limitations to our study. Firstly, in diagnosing DMDD, we used a parentreport assessment of DMDD symptoms. When assessing symptoms in children with ASD, a previous study had suggested that children with high functioning ASD (HFASD), who do not have intellectual disability, underreport their irritability symptoms[40]. In contrast, another study had suggested that both self-report and parent-report of irritability symptoms were reliable in male children with HFASD[41], revealing inconsistent findings. As such, in future studies, it may be useful to examine both self-reports and parent-reports. Secondly, irritability symptoms may have been dampened or hidden entirely since 10 children were already taking antipsychotics. However, 1 of 10 children taking antipsychotics also met diagnostic DMDD criteria as set forth in the DSM-5, and the other 9 children did not meet diagnostic DMDD criteria from before the initiation of their antipsychotics treatment to the time of symptom evaluation. Therefore, any effects on the results were considered small. Finally, this study was based on a clinical sample of children with ASD from a single institution, thereby warranting careful interpretation in the generalization of our results to all children with ASD.

Conclusion

In conclusion, the prevalence of children with ASD and DMDD was as high as approximately 17%, and they may have been likely to be over-estimated. ASD children with DMDD are more likely to have broad psychiatric problems, including depression and anxiety at a symptomatic level. Identifying DMDD in children with ASD may be helpful for the risk management of exacerbating symptoms of depression or anxiety, both at the time of assessment and in the future, and for the

development of appropriate therapeutic interventions. Since this is a cross-sectional study, further longitudinal studies are needed to both investigate in further depth the clinical course of children with ASD and to contribute to their appropriate treatment and intervention.

Acknowledgements

All authors have no COI to declare regarding the present study.

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