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Abstract

Background

In previous studies for children with pervasive developmental disorder (PDD), the prevalence for psychiatric comorbidities has varied because of their methodological differences. In this research, our PDD subjects were strictly limited by age and IQ scores, and we utilized a semi-structured interview to diagnose their coexisting disorders. The purpose of this study is to identify reliable prevalence and types of psychiatric comorbidities in children with high-functioning PDD (HFPDD).

Methods

The subjects were 49 children aged 6-15 years with HFPDD. In order to diagnose the comorbidities among them, we used the Japanese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version.

Results

Forty-eight cases (98%) met the criteria for at least one comorbidity. The median number of the present comorbidities per child was 2, and the mode was 2. Depression (37%), attention deficit hyperactivity disorder (49%), and oppositional defiant disorder (45%) were frequently observed.

Conclusions

Our finding indicates the high prevalence of comorbidities and the variety of the comorbid disorders in children with HFPDD. It is important to be aware of those comorbid disorders to provide the children with effective treatments.

Key Words: Pervasive developmental disorder; Comorbidity; Children; The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version

Introduction

Pervasive developmental disorder (PDD) is characterized by the core features, including deficient social interaction, impaired communication, and repetitive and stereotyped patterns of behavior,

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interest, and activities. PDD is frequently diagnosed based on behavioral criteria of Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-Ⅳ-TR)[1]. PDD in DSM-Ⅳ-TR includes autistic disorder (AD), Asperger's disorder (AS), and PDD not otherwise specified (PDD-NOS).

In addition to the core features, children with PDD often present various other symptoms such as emotional and behavioral problems, and they are less specific to PDD. However, it has been controversial whether these problems should be viewed as a separate comorbid disorder or a part of PDD symptom clusters[2]. There are also nosological problems for diagnosing psychiatric comorbidities in PDD. In DSM-Ⅳ-TR, some diagnoses, such as attention deficit hyperactivity disorder (ADHD), separation anxiety disorder (SAD), and generalized anxiety disorder (GAD), cannot be applied to patients with PDD[1].

It is difficult to diagnose the comorbid psychiatric disorders in PDD children since their communication skills are usually impaired to some degree[3]. Even the patients with adequate language skills have other types of communication problems. Moreover, they have impairments in "theory of mind", complex information processing, central coherence, and executive functioning[4-12]. These cognitive problems make it difficult for the children to describe their mental states, mental experiences, and even daily life experiences. Therefore, it can be challenging to determine if the patients' emotional and behavioral problems are due to the core features of PDD or a comorbid disorder superimposed on PDD. Because of this complexity, the precise prevalence of psychiatric comorbidities in PDD is poorly understood, and these coexisting disorders are often unrecognized in clinical settings.

On the other hand, the comorbid disorders cause significant loss of daily function in PDD children and extreme distress in their parents. Thus, reliable diagnoses of the comorbidities are very important for the patients and their families. If some problematic behaviors are recognized as signs of the comorbidities rather than isolated behaviors, more specific treatment will be possible for the children. As we often see in clinical experiences, specific treatments are more effective than the non-specific ones, and they can provide the children with greater improvement in functioning.

There are many studies of the psychiatric comorbidities in children with PDD[13-23]. However, they have many differences in the criteria for the disorder, the reasons for referral, and the age ranges of the subjects. Because of the lack of coherence in the methodologies, the prevalence of the comorbidity in those studies are very different from one another.

In general, children with a lower IQ (IQ <70) have a higher prevalence of mental illness than ones without a lower IQ[24]. If mentally-challenged children with PDD are included in a comorbidity study of PDD, it may have higher prevalence of the comorbidity than the study of only high-functioning PDD (HFPDD) children (IQ $\geqq 70$). For this reason, we targeted only HFPDD children. Moreover, the prevalence of comorbidities is highly affected by age of children. For instance, young children usually have a higher prevalence of SAD but a lower prevalence of schizophrenia compared to late adolescents. Since specific disorders appear more often in a particular age group[25], this study was limited to school-age children (6 to 15 years old).

Over recent decades, structured interviews have become more popular in both clinical settings and research fields. These interviews have helped clinicians and researchers to use standardized criteria. They have also helped researchers to figure out valid and reliable assessment methods in their studies. However, child and adolescent psychiatry in Japan has not placed a high value on using

structured and semi-structured interviews for diagnoses. Therefore, clinicians as well as empirical researchers in Japan have not been benefitted much from those diagnostic interviews. The Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (K-SADS-PL) is a semi-structured interview developed to make psychiatric diagnoses for patients aged 6-18 years. This diagnostic tool is known for its scrupulousness and high reliability[26]. In this study, we used the Japanese version of K-SADS-PL (K-SADS-PL-J). The purpose of this study is to identify reliable prevalence and types of psychiatric comorbidities in children with HFPDD by utilizing K-SADS-PL-J.

Methods

Subjects

The subjects were 49 HFPDD children. They were selected from consecutively referred children who received treatment at the child psychiatry outpatient clinic in Osaka City University Hospital between July 2007 and September 2010. Their age ranged from 6 to 15 years old (elementary and junior high school students).

At the outpatient clinic, the children were diagnosed after extensive diagnostic procedures. We strictly adhered to the diagnostic guidelines for PDD by (i) interviewing parents about their children's developmental history and any history of autistic behavior that their children exhibited since infancy via questionnaires; (ii) obtaining information from teachers via questionnaires about PDD; (iii) having the interviews carried out by more than two child psychiatrists who had experience with PDD examination and treatment, and (iv) observing the children's clinical course for more than 3 months.

The inclusion criteria for PDD included AD, AS, and PDD-NOS. The first two were diagnosed based on DSM-Ⅳ-TR criteria. However, PDD-NOS has no operational criteria in DSM-Ⅳ-TR[1], and it is defined as a residual category of PDD. For this reason, we used the Buitelaar and van der Gaag diagnostic criteria for the diagnosis of PDD-NOS. They require a total of three or more items from the criterion A for AD in DSM-Ⅳ-TR. Also, those items must include at least one item from the qualitative impairments in social interaction, which is a part of the criterion A[27].

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][28]) from our study. Children with severe neurological impairments or intractable epilepsy were also excluded.

Measures

For the purpose of diagnosing the comorbid psychiatric disorders in HFPDD children, we used the K-SADS-PL-J. With the simultaneous interview method, we confirmed that K-SADS-PL-J scored well on Cohen's kappa (ADHD=1.00, disruptive behavior disorders=0.91, anxiety disorders=0.76, tic disorders=0.75) for inter-rater reliability[29]. We also confirmed that it had concurrent validity for ADHD, disruptive behavior disorders, and anxiety disorders by using some other evaluation scales[29]. However, we made a couple of modifications on this diagnostic instrument. First, we used the K-SADS-PL-J only for the parents of the subjects. K-SADS-PL-J is designed to give semi-structured interviews to both children and their parents. As we discussed above, however, children with PDD mostly have difficulty in subjectively describing themselves, and it is hard to obtain dependable and appropriate information from them. Second, among mood disorders, we diagnosed only major depressive disorder and bipolar disorder. Others like dysthymic disorder and cyclothymic disorder were excluded. It is because some of their criteria are ambiguous[1], which makes it difficult for us to

collect reliable and valid data for these disorders. Last, we did not employ the exclusion criteria in DSM-Ⅳ-TR. DSM-Ⅳ-TR does not allow diagnosing SAD, GAD, social phobia, and ADHD in individuals with PDD[1]. However, these disorders are not universally present in PDD. Therefore, the validity of the exclusion criteria has been under discussion, and many previous studies[13-23] did not use the criteria.

Furthermore, we explained the purpose, the procedures, and the possible risks of the current research to the participants, as well as their alternatives to participation. We obtained written informed consent from all the subjects and their parents. This study was also reviewed and approved by the ethics committee at Osaka City University.

Statistical analyses

The statistical analyses were performed using SPSS 20.0J for Windows (SPSS Japan, Tokyo, Japan). With respect to comparison between the three groups (i.e., children with AD, AS, and PDD-NOS), when the data were normally distributed, one-way analysis of variance was used for continuous variables and Kruskal-Wallis test was used when the data were not normally distributed. And we used χ^2 test for categorical data comparisons. The level of statistical significance was set at 0.05 (two-tailed).

Results

Table 1 shows the demographic data of the participants. Forty-nine children were diagnosed with HFPDD (36 males and 13 females). The mean age was 11.2 years, and the mean of full-scale IQ score on the WISC-Ⅲ was 95.7. Among the subjects, 6.1% had public assistance, and 24.5% had their biological father or mother absent. The subjects consisted of 24 children with AD, 4 with AS, and 21 with PDD-NOS. There were no statistically significant differences in age (p=0.812), Full IQ (p=0.251), Verbal IQ (p=0.762), and Performance IQ (p=0.064) between the three groups. The gender distribution was also similar in these groups (p=0.403).

Table 2 shows the prevalence of the present and lifetime comorbidities. Forty-eight cases (98%) met criteria for at least one comorbidity for both present and lifetime diagnoses.

The prevalence of the present diagnosis of major depressive disorder was 36.7%. None of the children met criteria for bipolar 1 or bipolar 2 disorder.

Although no participants fulfilled the criteria for schizophrenia, 10.2% of the subjects had

Table 1. Characteristics of the children with HFPDD

	Total subjects n=49	AD n=24	AS n=4	PDD-NOS n=21	p
Age (years: mean (SD))	11.2 (2.5)	11.4 (2.6)	11.5 (1.7)	11.0 (2.6)	0.812[b]
Male /Female (n (%))	36 (73.5) / 13 (26.5)	17 (70.8) / 7 (29.2)	2 (50.0) / 2 (50.0)	17 (81.0) / 4 (19.0)	0.403[a]
Full IQ (mean (SD))	95.7 (13.1)	94.2 (11.4)	88.7(9.1)	98.8 (15.4)	0.251[c]
Verbal IQ (mean (SD))	100.5 (12.9)	99.1 (12.6)	100.7 (0.6)	102.1 (14.9)	0.762[c]
Performance IQ (mean (SD))	92.5 (15.1)	90.3 (13.7)	77.7 (17.0)	98.4 (14.4)	0.064[b]
Public assistance (n (%))	3 (6.1)	2 (8.3)	0	1 (4.8)	0.766[a]
Absence of one's father or mother (n (%))	12 (24.5)	5 (20.8)	2 (50.0)	5 (23.8)	0.477[a]

HFPDD, high-functioning pervasive developmental disorder; AD, autisic disorder; AS, asperger's disorder; and PDD-NOS, pervasive developmental disorder not otherwise specified. [a]χ^2 test. [b]one-way analysis of variance. [c]Kruskal-Wallis test.

psychotic disorder not otherwise specified for the present diagnosis. Each of these children had only one psychotic symptom including delusions and hallucinations.

Fifty-seven percent of the children had at least one anxiety disorder. Generalized anxiety disorder had the highest prevalence of the present diagnosis (26.5%) among anxiety disorders. The prevalence of social phobia was 22.4%, and it was followed by specific phobia (16.3%), obsessive compulsive disorder (OCD) (14.3%), SAD (10.2%), panic disorder (8.2%), and posttraumatic stress disorder (2.0%).

The most common present DSM-Ⅳ-TR diagnosis was ADHD (49.0%). Fifty-eight percent of the ADHD children had the combined sub-type. Only one case (4%) had the hyperactive sub-type.

Oppositional defiant disorder (ODD) was also common comorbidity in our subjects (44.9%). The prevalence of conduct disorder (CD) was 14.3%.

The prevalence of the present diagnosis was 6.1% for enuresis and 4.1% for encopresis. However, these prevalence for the lifetime diagnosis were 20.4% and 12.2%, respectively.

Anorexia nervosa was observed in 6.1%. Other eating disorders such as bulimia nervosa were not found in our study.

Although none of the subjects had transient tic disorder for the present diagnosis, it was observed in 10.2% for the lifetime. The prevalence of tic chronic disorder was 6.1% for the present and 10.2% for the lifetime. Tourette's disorder was found in 8.2% for both present and lifetime.

Table 2. K-SADS-PL-J diagnoses in 49 children with HFPDD

	Present diagnosis		Lifetime diagnosis	
	n	(%)	n	(%)
Any diagnosis	48	98.0	48	98.0
Major depressive disorder	18	36.7	21	42.9
Psychotic disorder not otherwise specified	5	10.2	5	10.2
Any anxiety disorder	28	57.1	28	57.1
Panic disorder	4	8.2	4	8.2
Separation anxiety disorder	5	10.2	8	16.3
Social phobia	11	22.4	12	24.5
Specific phobia	8	16.3	8	16.3
Generalized anxiety disorder	13	26.5	14	28.6
Obsessive compulsive disorder	7	14.3	7	14.3
Posttraumatic stress disorder	1	2.0	1	2.0
Enuresis	3	6.1	10	20.4
Encopresis	2	4.1	6	12.2
Anorexia nervosa	3	6.1	3	6.1
ADHD	24	49.0	26	53.1
ADHD subtypes				
Inattentive	9	18.4	10	20.4
Hyperactive	1	2.0	1	2.0
Combined	14	28.6	15	30.6
Oppositional defiant disorder	22	44.9	26	53.1
Conduct disorder	7	14.3	7	14.3
Transient tic disorder	0	0.0	5	10.2
Chronic motor or vocal tic disorder	3	6.1	5	10.2
Tourette's disorder	4	8.2	4	8.2

K-SADS-PL-J, The Japanese version of the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version; HFPDD, high-functining pervasive developmental disorder; and ADHD, attention deficit hyperactivity disorder.

Figure 1 shows the frequencies of multiple comorbidities in the HFPDD children for the present and lifetime diagnoses. The median number of the present comorbidities per child was 2, and the mode was 2 (28.6%). Among the subjects, 75.5% of the children had more than one present comorbidity. The AD, AS, and PDD-NOS groups did not significantly differ in the number of comorbidities for the present and lifetime (present: p=0.446, lifetime: p=0.200).

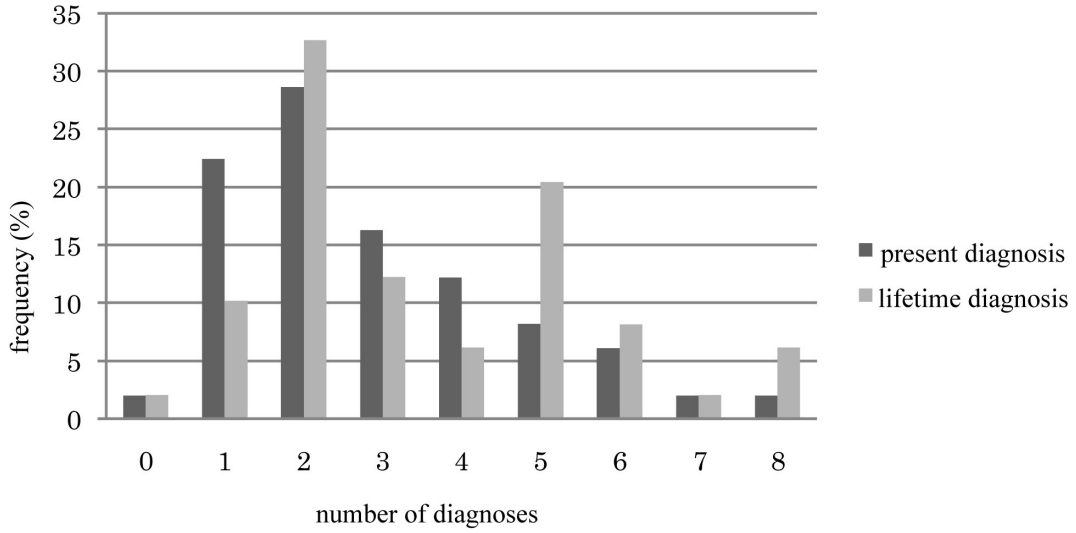


Figure 1. Frequency of the number of psychiatric comorbidity of the 49 children with pervasive developmental disorder.

Discussion

Our study confirmed the frequent co-occurrence of HFPDD with other psychiatric disorders. Ninety-eight percent of the children had at least one DSM-Ⅳ-TR psychiatric disorder in addition to HFPDD. Moreover, 75.5% of the subjects had more than one comorbid disorder. Our findings, the high prevalence of comorbidities in HFPDD children, correspond to the previous studies including Mattila et al's one[13-23].

Considering the difference of the prevalence of comorbidities of the children with PDD among previous studies[13-23], we limited our subjects to school-age children (6 to 15 years old) with HFPDD and employed the semi-structured interview. As far as we know, Mattila et al's study in Finland is the only research which has systematically used structured or semi-structured interviews to diagnose coexisting disorders in HFPDD children. Thus, this paper is the first ever research paper about comorbidities in HFPDD children by using semi-structured interviews in Asian countries.

Mood disorders were reported at high prevalence in case of children with PDD, and several researchers suggested that depression is the most frequent disorder[14-18,20,21]. In our study, the prevalence of the present diagnosis of major depressive disorder was 36.7%. The prevalence of depression in PDD children has been reported between 1.4% to 57.5%[13-18,22]. Simonoff et al reported the lowest prevalence[16]. It could have been because they used a population-derived sample which was not targeted in our study. Ghaziuddin et al[21] presumed that the prevalence of depression in children with PDD and related disorders might increase with age. This presumption could explain to some extent why there was a difference in the reported prevalence. Similar to some of the previous studies, our study showed a high prevalence of major depression in PDD children.

None of the children met the criteria for bipolar 1 or bipolar 2 disorder in our study. Reported

prevalence of bipolar disorder in PDD children was varied in previous studies[13,16-18,22,23]. Some researchers found the high prevalence ranging from 21% to 27%[18,23]. On the other hand, no bipolar disorder in PDD children was reported in our study as well as other studies, including the one by Mattila et al[13,16,21]. Diagnosing bipolar disorders can be difficult particularly in the context of PDD. Some children with PDD often laugh even though the situation is not really funny. In addition, their emotions tend to be quite reactive, poorly modulated, and fluctuate minute by minute with what is occurring around them. These emotional tendencies have not been systematically studied yet, and the neurobiological basis of PDD is still unknown. Because of these characteristics of PDD, we consider that bipolar disorders in PDD children might have been overdiagnosed in the previous study which showed a high prevalence.

No children in this study met the criteria for schizophrenia, because the onset of schizophrenia is usually in late adolescence or adulthood[30]. However, 10.2% of the children had psychotic disorder not otherwise specified for the present diagnosis. Each of these children had only one psychotic symptom including delusions and hallucinations. Poulton et al[31] reported that schizophreniform disorder in adulthood was predicted based on the psychotic symptoms observed at age 11. These symptoms may be warning signs for future psychotic episodes, and if so, it becomes very important to identify them among children.

Fifty-seven percent of the subjects suffered from at least one comorbid anxiety disorder. The prevalence of anxiety disorder in Mattila et al's study was 45%[13]. All the other studies which systematically assessed PDD children also reported high prevalence[14-19].

In our study, GAD was the most common anxiety disorder in children with PDD (26.5%). Other studies reported relatively low prevalence of this disorder although the prevalence varied between 2.4% to 22.7%[14-19]. Anxiety in PDD children should be examined very carefully since they easily become anxious in changing environments and new situations. However, our subjects presented various anxiety symptoms which cannot be explained only by their vulnerability to new situations. Thus, GAD in PDD children would have been underdiagnosed in previous works if those atypical anxiety symptoms had been missed.

Our prevalence of social phobia was 22.4%. The prevalence reported in the past ranged from 2.5% to 29.2%[13-19]. It is pointed out that a lack of interest in other people is one of the core symptoms of PDD. When PDD children do not interact enough with others, it is difficult to judge whether the lack of interaction results from social phobia or the core symptom of PDD. However, many children with PDD are not aloof, and they have interest in other people. Therefore, the core symptom of PDD cannot be the only reason for the high prevalence of social phobia in this study.

Specific phobia was found in 16.3% of our subjects. Animal type was the most frequently observed phobia in our study (4 cases, 50%). The prevalence in previous works varied between 8% to 44%[13-19]. Leyfer et al[14] reported that the prevalence was 44%, and that fear of sound was the most frequently observed. The prevalence of specific phobia in Mattila et al's study was 28%, and they did not find any fear of sound[13]. Recent studies indicate that some of PDD children have hyperesthesia, especially acoustic hyperesthesia, at high prevalence[32-36]. Because of their sensitivities, they sometimes show strong anxiety and strain when they hear a loud sound. On the other hand, children with a phobia have avoidance or anxious anticipation of feared objects or situations. PDD children should be carefully assessed for a phobia because of their great fear of a loud sound as the nature of PDD. Since hyperesthesia was not examined in Leyfer et al's study, their prevalence of phonophobia might have

become higher than it was supposed to be.

The prevalence of OCD was 14.3% in our subjects. The prevalence of OCD in PDD children ranged 6.4% to 37.2% in other studies[13-17,19]. It is hard to clearly distinguish ritual behaviors in PDD from ones in OCD, which could explain the wide range of the OCD prevalence in PDD. When the subjects had ego-syntonic repetitive behaviors which were obviously recognized as PDD symptoms, we did not diagnosed them with OCD in this study.

Forty-nine percent of the children met the criteria for ADHD for the present diagnosis. Our high prevalence of ADHD are consistent with other reports on PDD children including Mattila et al's study[13-18]. DSM-Ⅳ-TR does not allow the additional diagnosis of ADHD in children with PDD[1]. However, the findings in our study, as well as others, suggest that ADHD syndromes are not universal but common comorbidities in PDD children. Thus, the exclusion criteria in DSM-Ⅳ-TR should be reconsidered. It is important to recognize the high prevalence of ADHD in individuals with PDD, because ADHD may impede their learning in school and everyday life.

In the current study, the prevalence of ODD was 44.9%, which was higher than the prevalence of CD (14.3%). This result is similar to previous works[13-18]. However, Leyfer et al[14] reported lower prevalence of ODD (7%). It is unclear whether the inconsistent results primarily stem from the different criteria or subjects they used. Only Green et al's study[37] had high prevalence for both CD and ODD (25% for each). This result could have reflected the referral bias in their study, which compared CD with PDD in adolescents.

Our results should also be interpreted in the context of the following methodological limitations. Mattila et al's study is the only research which has systematically examined the prevalence of the comorbidity in HFPDD children by using structured or semi-structured interviews. Therefore, the previous studies with which we compared our results targeted not only HFPDD children but also various age groups with a wide range of IQ scores. Besides, their diagnostic methods for the comorbid disorders were not necessarily the same as ours. Thus, there is a limit to comparing our results to theirs. We hope that the number of comorbidity studies restricted to HFPDD children will grow. In addition, the subjects were selected from only one outpatient clinic, which might have limited the generalizability of the results. Severe cases tend to visit our clinic because of the nature of the university hospital. For this reason, the prevalence of the comorbidity could be higher than the ones in other types of medical facilities. Therefore, multi-center studies, which contain more representative samples, are needed for the future studies. Furthermore, since we performed K-SADS-PL only on the parents, the collected information might not have been enough to assess the comorbidities in HFPDD. Because children with HFPDD have a hard time verbally explaining their own situations, clinical assessments based on their interviews are difficult. Thus, only the parents were targeted for K-SADS-PL in this study. Moreover, the number of our subjects was not sufficient enough to compare the prevalence of the comorbidity between three groups: AD, AS, and PDD-NOS. The number of subjects should be increased for group comparisons.

In conclusion, we found the high prevalence of comorbidities and the variety of the comorbid disorders in HFPDD. We also found that many of the HFPDD children had more than one comorbidity. These coexisting disorders are often underdiagnosed in clinical settings since HFPDD children have difficulty in talking about their symptoms and situations. Therefore, it is very important to be aware of those comorbid disorders for the treatments and researches. This study indicates that it is necessary to actively examine comorbidities in HFPDD, and that semi-structured

interviews are suitable for the examination.

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