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Prevalence of Comorbid Attention Deficit Hyperactivity Disorder (ADHD) in Chinese Hong Kong Children with Autism Spectrum Disorder (ASD)

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Abstract

Comorbid Attention Deficit Hyperactivity Disorder (ADHD) in children with Autism Spectrum Disorder (ASD) was previously not recognized by the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) and the International Classification of Diseases–Tenth edition (ICD-10). There had been new understanding concerning these two disorders lately, hence the newly published Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) had finally allowed ADHD to be diagnosed in the course of ASD as a comorbid disorder. Early detection is deemed necessary as ADHD is known to be readily responsive to medication and have many serious impacts if untreated; however, there is a lack of local studies to investigate the prevalence and clinical profile of this group of ASD children with comorbid ADHD.

Our study aimed to examine the prevalence of comorbid ADHD in ASD children who attended a local child psychiatry clinic and to explore the clinical pattern in this group of ASD children. A total of 101 children aged 6-11 years old with ASD diagnosis were recruited and was subsequently assessed for comorbid ADHD.

The result shows that 48.5% i.e. nearly one in every two ASD children that comes to our clinic were suffering from comorbid ADHD. This is significantly higher than the prevalence in local general population. We also found a lack of apparent difference in the clinical presentation in ASD children with or without comorbid ADHD, implying imperative need for clinicians to routinely screen for comorbid ADHD in every ASD children.

Keywords: Autism spectrum disorder; Comorbidity; Attention deficit hyperactivity disorder; Hong kong children

Introduction

Historical background of ADHD features in children with ASD

Features of inattention and hyperactivity had long been observed in children with Autism Spectrum Disorder (ASD), yet these features were once believed to be due to mere phenotypic mimicry of ASD features according to earlier studies [1-6], hence Attention Deficit Hyperactivity Disorder (ADHD) had not been recognized as a comorbid diagnosis in ASD children according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) [7] and the International Classification of Diseases– Tenth edition (ICD-10) [8].

However, recent research showed increasing evidence supporting ADHD to co-exist in ASD children as a comorbid disorder instead of due to phenotypic mimicry as from earlier studies. Firstly, Ghanizadeh [9] and Ronald, Larsson, Anckarsäter and Lichtenstein [10] both demonstrated with factor analysis among ASD children with ADHD features that ASD items and ADHD items fall into two separate factor models. This suggests that ADHD features are distinct from ASD features in this group of children. Secondly, it was demonstrated in neuropsychological studies that ASD children with ADHD features shared impairments of both disorders, i.e. inhibition and sustained attention which are evidenced to be major impairment in ADHD and cognitive flexibility, which is evidenced to be major impairment in ASD; while children with ASD only had deficits in cognitive flexibility, and inhibition and sustained attention were unimpaired [11-13]. This further suggests that ADHD co-exists with ASD as an independent disorder with distinct neuropsychological profile. Lastly, treatment trials in ASD children with ADHD features showed that methylphenidate was effective in treating ADHD symptoms without affecting the core symptoms of ASD, and the effectiveness in treating the ADHD symptoms was as effective as for those with ADHD only [14-16]. This consolidates the postulation that ADHD symptoms in ASD children represent a separate disorder entity rather than being part of the ASD presentation. All in all, these had led to changes in our understanding of ADHD in ASD children as introduced by the newly published Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5) – ADHD is now allowed to be diagnosed in the course of ASD as a comorbid condition [17].

Prevalence of ADHD in ASD children

Since the recognition is allowed, many literatures had found that

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comorbid diagnosis of ADHD is common among ASD children. It was quoted that among ASD children, 28% to 78% has a comorbid diagnosis of ADHD [5,9,18-23], which is much higher than the prevalence of ADHD among typically developing children (3 to 7% from the American Psychiatric Association prevalence study [24], and 6.1 to 9% from our local study [25]. And from research that had looked further into the ADHD presentation among this group of ASD children, the overall symptomatology of ADHD in ASD children appears to be similar to that in children with ADHD only [9,18,22-23,26-31]. Despite much is known about ADHD presentation in ASD children with comorbid ADHD, little is explored to date on the ASD clinical profile in this group of children, such as whether certain ASD symptoms are associated with increased comorbidity with ADHD.

ASD symptom association with ADHD

Although limited studies had looked into ASD symptomatology in ASD children with comorbid ADHD, there were two large-scaled Sweden community twin studies worth noting. Ronald et al.10 and Polderman, Hoekstra, Posthuma, and Larsson 32 had explored the association of ASD symptom domains with ADHD symptom domains in 17,000 and 17,770 twins. Both demonstrated from their studies that Restricted and Repetitive Behaviors (RRB) is strongly associated with all ADHD symptom domains; Poldermanet al [32]. even put forward that RRB had strong correlation with ADHD symptoms not only phenotypically, but also genetically. However, this association is yet to be confirmed in children with ASD. If more RRB symptoms are identified in ASD children with comorbid ADHD compared to those without ADHD, this clinical profile may alert early detection of ASD children who have higher chance of developing comorbid ADHD.

Impact on ASD children if ADHD is left undiagnosed and untreated

Despite the high prevalence of ADHD in children with ASD, ICD-10 and DSM-IV classification systems had previously assumed a hierarchical standpoint when dealing with ASD and ADHD – i.e. the diagnosis of ASD automatically overrides the diagnosis of ADHD. This had led to ADHD in many ASD children to be left unrecognised and underdiagnosed – and eventually untreated [33]. Significant number of adults with ASD was found to have undiagnosed ADHD: Johnston et al [34]. Reported 37% of adults with ASD had significant ADHD symptoms, while Hofvander, et al [35]. reported 43% ASD adults had comorbid diagnosis of ADHD. Among the adults recruited in both studies, all were not previously diagnosed of ADHD during childhood.

In addition to general impacts of untreated ADHD, untreated ADHD was shown to have significant impact on the overall outcome in ASD children as well. It had been reported that ASD children who have comorbid ADHD would have poorer adaptive functioning, daily living skills, global executive control and quality of life compared with ASD children without comorbid ADHD [36-39]. The studies also found that ASD children who have comorbid ADHD had significantly more social impairment than ASD children without ADHD [36-39]. Furthermore, Antshel, et al [40]. suggested that comorbid ADHD might hinder ASD social training outcome as among three groups of ASD children (ASD only, ASD with comorbid anxiety and ASD with comorbid ADHD) that received 10 sessions of group social skills intervention together, groups that had ASD only and ASD with comorbid anxiety showed significant improvement after treatment while the group of ASD children with comorbid ADHD was the only group that showed no improvement.

Despite the high prevalence and the detrimental impacts of untreated ADHD in ASD children which are proven to respond readily to effective treatment, world-wide publications on ADHD in ASD children is still limited; and no local data on the prevalence of ADHD in children with ASD in Chinese Hong Kong population is available at the moment. Also, little is known on the clinical pattern in this group of children. Therefore, there is pressing need for a local study to identify the prevalence of ADHD in Chinese Hong Kong ASD children and to alert clinicians in our locality of the clinical profile and associated factors of this group of children which could aid early detection and treatment.

Objectives

We aim to examine the prevalence and clinical pattern of ADHD in Chinese Hong Kong children with ASD. Firstly, based on epidemiological data to date, we predict that the prevalence of ADHD in ASD children will be higher than that in general population. Secondly, upon examining the clinical pattern especially ASD presentation, we hypothesize thatASD children with comorbid ADHD would have more Restricted and Repetitive Behaviors (RRB) compared to those without ADHD.

Methods

Participants

We recruited children aged6 to 11 years old from consecutive new referrals to the child psychiatry out-patient clinic in Alice Ho Miu Ling Nethersole Hospital (AHNH) from September 2014 to December 2015. The hospital serves the New Territories East area of Hong Kong, with a population of 1.3 million which is approximately one sixth the local population [41]. Ethical approval was obtained from the relevant institutional board on human subjects.

To minimize recall bias, the AHNH child psychiatry out-patient new case list was the sampling frame. All subjects were seen by child psychiatrists in routine services and included if a working diagnosis of ASD was made. They were all 6 to 11 years old who were studying at local mainstream primary school. Exclusion criteria included children who are suffering from intellectual disability, acute severe mental illness e.g. mania and psychosis, or severe neurological illnesses including epilepsy, cerebral palsy, or medical illness which requires long term medications, and primary caretaker who does not understand Chinese.

Procedures

Subjects were recruited only if the parents or caregivers provide written Chinese consent. The parents were then first interviewed with the Developmental, Dimensional and Diagnostic Interview (3Di) [42] to confirm the diagnosis of ASD. For those with ASD diagnosis confirmed by 3Di, a further assessment with the Diagnostic Interview Schedule for Children – Version IV (DISC-IV) ADHD module would then be proceeded for assessment of ADHD diagnosis on the same day. To evaluate associated socio-demographic factors, subject's personal and family data wascollected using a demographic questionnairefilled in by the caretaker. Strengths and Difficulties

Questionnaire (SDQ)-parent version was also collected to evaluate subject's other clinical behaviors and assess the impact in various settings. Since the Strengths and Weaknesses of ADHD-symptoms and Normal-behaviors questionnaire (SWAN)-parent version, a tool assessing children's ADHD symptoms, had been distributed routinely to all children first attending the clinic regardless of the diagnosis, we retrieved and compared all SWAN questionnaires for participants and non-participants for our study to assess for responder bias.

Measures

Developmental, Dimensional and Diagnostic Interview (3Di): The 3Di is a computerized semi-structured parent-report interview designed to assist diagnosis and provide dimensional scores of ASD among children with normal intelligence. It provides dimensional scores on three domains: social reciprocity, communication and restricted and repetitive behaviors. Research demonstrated 3Di to have strong psychometric properties. Inter-rater and test-retest reliability are high, with intraclass correlation coefficients greater than 0.86 for all dimensional scores. Discriminant validity is excellent as the instrument managed to discriminate ASD from non-ASD children with positive predictive power 0.93 and negative predictive power 0.91. Criterion validity is high when compared with another gold standard Autism Diagnostic Interview-Revised (ADI-R): 100% agreement for communication, 86% for social reciprocity and 76% for repetitive and restricted behaviors [42].The 3Di has also been translated into local Cantonese version and validated locally [43]. Results found excellent reliability and validity, and achieved a sensitivity of 95% and specificity of 77%. The study included a group of ASD children with comorbid ADHD and reported results not affected by the presence of comorbid ADHD compared to children with ASD only.

Diagnostic interview schedule for Children – Version IV (DISC-IV), parent version, ADHD module

DISC-IV is a highly structured respondent-based diagnostic interview schedule originally designed for use by non-clinician in large scale epidemiological surveys to assess psychiatric diagnosis in children and adolescent upon a 12-month time-frame. There are six modules covering more than 30 psychiatric diagnoses in childhood. The ADHD module was used in this study. We followed the recommendation by the DISC Development Group that an impairment score of three, equivalent to one severe or at least two intermediate impairments in six domains of daily function, is considered to be clinically significant. There is literature supporting good reliability and validity of its various versions, including a translation in Cantonese for the use in Hong Kong in diagnosing ADHD with parent reported version [44,45]. Most importantly, DISC-IV ADHD module had been widely used in international and local published studies to diagnose ADHD in children with ASD [46-48].

Strengths and Difficulties Questionnaire (SDQ), parent version: The SDQ is a 25-item behavioral screening questionnaire divided into five subscales (Hyperactivity, Emotional Symptoms, Conduct Problems, Peer Problems and Prosocial Behaviors). Each item is rated under a three point system scoring 0 when the statement is rated "not true", 1 when rated "somewhat true" and 2 when rated "certainly true". Five of the items were rated reversely [49,50]. A large scale community study in Britain found that the SDQ symptom scores closely predict the prevalence of clinician rated child psychiatric disorders [51], and the odds of developing a disorder increased at a constant rate across the full range of scores, confirming the questionnaire's dimensional nature [52] Lai et al. [53] also translated the SDQ into Chinese version and confirmed its reliability and validity in Hong Kong Chinese children. To understand children's difficulties in more clinical perspectives, the difficulty subscales can be further

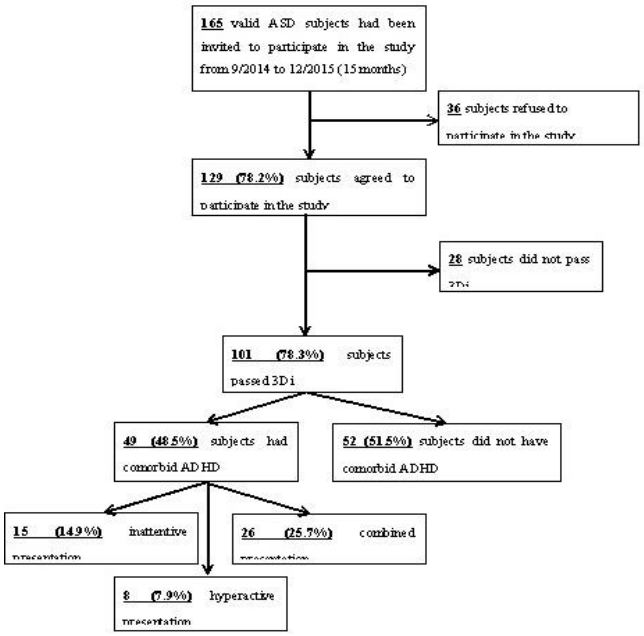

Figure 1: Flow chart of the recruitment process.

Table 1: Basic socio-demographic information of recruited subjects.

	N (%)
Gender (Child)	
Male	90 (89.1%)
Female	11 (10.9%)
Child current Age (Mean ± SD)	7.93 ± 1.47
6	16 (15.8%)
7	33 (32.7%)
8	18 (17.8%)
9	16 (15.8%)
10	12 (11.9%)
11	6 (5.9%)
Current grade	
P1	26 (25.7%)
P2	25 (24.8%)
P3	24 (23.8%)
P4	13 (12.9%)
P5	11 (10.9%)
P6	2 (2.0%)
Father's current Age (Mean ± SD)	**44.22 ± 7.2**
Mother's current Age (Mean ± SD)	**39.96 ± 4.67**

Table 2: Comparison between ASD+ADHD group and ASD ONLY group in child's characteristics.

Child's Characteristics	ASD+ADHD (n=49)	ASD ONLY (n=52)	p-value
Gender			**0.393[c]**
Male	45 (91.8%)	45 (86.5%)	
Female	4 (8.2%)	7 (13.5%)	
Child's current age	**7.84 ± 1.43**	**8.02 ± 1.5**	**0.534[t]**
(Mean ± SD)			
Current grade			**0.734[c]**
P1	12 (24.5%)	14 (26.9%)	
P2	14 (28.6%)	11 (21.2%)	
P3	12 (24.5%)	12 (23.1%)	
P4	7 (14.3%)	6 (11.5%)	
P5	3 (6.1%)	8 (15.4%)	
P6	1 (2%)	1 (1.9%)	

*p<0.05; [c] – Chi-square test; [t] – Independent-samples t test

clustered into Internalizing and Externalizing Behaviors. Moreover, both Western and local studies had further proven the extended version of SDQ with an impact supplement sheds light on the child's functional impairment [54,55]. Therefore, we decided to use the SDQ extended version in our study to capture the other clinical behaviors and impact of comorbid ADHD in our sample of ASD children.

Strengths and Weaknesses of ADHD-symptoms and Normal-behaviors questionnaire (SWAN), parent version: SWAN questionnaire was developed from the Swanson, Nolan, and Pelham (SNAP) Rating Scale without changing the content, but rewording the scoring scale in order to capture both the strength and the weakness of each item. It covers 18 items of ADHD, with nine ADHD-Inattentive items and nine ADHD-Hyperactive/Impulsive items. Each item is rated under a seven point system from "far below average" (+3) to "far above average"(-3) relative to children of the same age. This change in covering both the positive and negative ends of ADHD allows for a more dimensional understanding of ADHD presentation. This aims to overcome the problem of over-focusing the presence of problem behavior and hence risk of skew-ness of result leading to over-identification of ADHD [56]. SWAN has been validated locally with good psychometric property in typically developing children. Internal consistency was high, yielding Cronbach's alpha over 0.9 for both parent and teacher versions for the subscales and the Area Under Curves (AUCs) for both sex and subscales were well above 0.8 [57].

Statistical methods

SPSS version 22 was used for statistical analyses (SPSS Inc., Chicago, IL, USA). We compared the differences between groups of children with ASD only and ASD with comorbid ADHD in socio-demographic information, 3Di scores and SDQ symptom and impact scores using Chi Square test/ Fisher's Exact test for categorical data and independent sample t-test for continuous data. We also compared the differences between groups of ASD participants and non-participants in age, gender and SWAN parent version total scores using Fisher's Exact test and independent sample t-test. Logistic regression was further conducted to study the relationship between ADHD (dependent variable) with variables which were found to

Table 3: Comparison between ASD+ADHD group and ASD ONLY group in father's characteristics.

Father's Characteristics	ASD+ADHD (n=49)	ASD ONLY (n=52)	p-value
Father's current Age (Mean ±SD)	**43.04 ± 7.64**	**45.33 ± 6.64**	**0.111[t]**
Father's age at child birth (Mean ± SD)	**35.2 ± 7.43**	**37.31 ± 6.71**	**0.138[t]**
Father's education level			***0.029[f]**
Primary or less	5 (10.2%)	1 (1.9%)	
Secondary	27 (55.1%)	22 (42.3%)	
Post-secondary	6 (12.2%)	4 (7.7%)	
University or above	11 (22.4%)	25 (48.1%)	
Father's job			**0.096[f]**
Managers & Administrators	4 (8.2%)	8 (15.4%)	
Professionals	4 (8.2%)	10 (19.2%)	
Associate Professionals	9 (18.4%)	14 (26.9%)	
Clerks	3 (6.1%)	6 (11.5%)	
Service Workers and Shop Sales Workers	11 (22.4%)	2 (3.8%)	
Craft and related Workers	4 (8.2%)	2 (3.8%)	
Plant and Machine Operators	3 (6.1%)	3 (5.8%)	
Elementary Occupations	2 (4.1%)	1 (1.9%)	
Self-employed	1 (2.0%)	0 (0.0%)	
Unemployed	5 (10.2%)	4 (7.7%)	
Retired	0 (0.0%)	1 (1.9%)	
Occupations not classifiable	3 (6.1%)	1 (1.9%)	

*p<0.05; [f]- Fisher's exact test; [t] – Independent-samples t test

Table 4: Comparison between ASD+ADHD group and ASD ONLY group in mother's characteristics.

Mother's Characteristics	ASD+ADHD (n=49)	ASD ONLY (n=52)	p-value
Mother's current Age (Mean±SD)	**38.86 ± 4.76**	**41 ± 4.38**	***0.02**[t]
Mother's age at child birth (Mean ± SD)	**31.02 ± 4.5**	**32.98 ± 4.32**	***0.028**[t]
Mother's education level			**0.159**[f]
Primary or less	2 (4.1%)	1 (1.9%)	
Secondary	30 (61.2%)	27 (51.9%)	
Post-secondary	9 (18.4%)	6 (11.5%)	
University or above	8 (16.3%)	18 (34.6%)	
Mother's job			**0.754**[f]
Managers & Administrators	0 (0.0%)	2 (3.8%)	
Professionals	6 (12.2%)	7 (13.5%)	
Associate Professionals	5 (10.2%)	5 (9.6%)	
Clerks	7 (14.3%)	6 (11.5%)	
Service Workers and Shop Sales Workers	6 (12.2%)	3 (5.8%)	
Plant and Machine Operators	0 (0.0%)	1 (1.9%)	
Housewives	25 (51.0%)	28 (53.8%)	

*p<0.05; [f]- Fisher's exact test; [t] - Independent-samples t test

Table 5: Comparison of Developmental, Dimensional and Diagnostic Interview (3Di) between ASD+ADHD group and ASD ONLY group.

3Di Domains	ASD+ADHD (n=49)	ASD ONLY (n=52)	p-value
Social reciprocity	16.5 ± 3.83	16.08 ± 3.34	0.559[t]
Communication	14.05 ± 3.26	13.41 ± 2.67	0.287[t]
Repetitive Restricted Behaviors (RRB)	4.55 ± 1.43	4.31 ± 1.48	0.403[t]

*p<0.05; [t] -Independent-samples t test

Table 6: Comparison of Strengths and Difficulties Questionnaire (SDQ) parent version difficulties between ASD+ADHD and ASD ONLY group.

SDQ difficulties (Parent version)	ASD+ADHD (n=49)	ASD ONLY (n=52)	p-value
Total Difficulties Score	**21 ± 5.28**	**16.98 ± 5.28**	***<0.001**[t]
Prosocial	5.43 ± 1.99	5.37 ± 2.05	0.839[t]
Hyperactivity	8.06 ± 1.65	5.85 ± 2.02	***<0.001**[t]
Emotional symptoms	3.9 ± 2.08	3.77 ± 2.63	0.483[t]
Conduct problem	4.12 ± 2.08	2.9 ± 1.35	***0.004**[t]
Peer problems	4.9 ± 1.9	4.46 ± 2.17	0.178[t]
Externalizing	12.2 ± 3.21	8.75 ± 2.59	***<0.001**[t]
Internalizing	8.8 ± 3.09	8.23 ± 4.13	0.218[t]

*p<0.05; [t]– Independent-samples t test

Table 7: Comparison of SDQ impact scores between ASD+ADHD group and ASD ONLY group.

Impact (Parent report)	ASD+ADHD (n=49)	ASD ONLY (n=52)	p-value
Total Impact score	**5.45 ± 2.62**	**3.48 ± 2.64**	***<0.001**[t]
Child distress	1.27 ± 0.7	0.92 ± 0.68	***0.022**[t]
Home impact	0.96 ± 0.64	0.67 ± 0.68	***0.023**[t]
Friendships impact	0.86 ± 0.74	0.67 ± 0.71	0.203[t]
Classroom impact	1.43 ± 0.68	0.71 ± 0.75	***<0.001**[t]
Leisure activity impact	0.94 ± 0.78	0.5 ± 0.7	***0.003**[t]

*p<0.05; [t]– Independent-samples t test

have significant differences (P < 0.2) in univariate analysis. Age and gender were both controlled in regression studies. All candidate variables were put into the model with backward elimination method. Forwardelimination method was further used to double check. Intraclass correlation coefficient is used to assess inter-rater reliability between the two raters for 3Di. All statistical tests were two tailed and p value of <0.05 was considered significant. Results were expressed as mean ± standard deviationfor all continuous data.

Results

A total of 165 parents were approached, but only 129 parents provided written consent. Of the 36parents who refused to participate, age, gender and SWAN total score of the children were statistically insignificant compared to our sample group (Table 9). The sample finally consisted of 101 children whose ASD diagnosis was confirmed by 3Di (Figure 1). The intraclass correlation coefficients (ICC) for all three subscales for 3Di between the two raters are over 0.9, the inter-rater reliability is therefore satisfactory. The mean age of the children

Table 8: Logistic regression analysis of significant risk factors for presence of ADHD in ASD. Significant findings only:

Risk factor	Unadjusted odds ratio (OR) (95% CI)	Adjusted odds ratio (OR) (95% CI)	p-value
Father's educational level	0.57	0.57	0.007
	(0.378-0.859)	(0.36-0.862)	

Hosmer and Lemeshow goodness-of-fit test; Chi-square statistics: 1.64; df=2; p-value=0.441

Table 9: Comparison between participants and non-participants in child's characteristics and SWAN parent version total score.

	Participants (n=101)	Non-participants (n=36)	p-value
Child's gender			**1[f]**
Male	90 (89.1%)	33 (91.7%)	
Female	11 (10.9%)	3 (8.3%)	
Child current Age	**7.93 ± 1.47**	**7.5 ± 1.44**	**0.131[t]**
SWAN total score	**16.27 ± 16.3**	**11.14 ± 16.98**	**0.111[t]**

*p<0.05; [f]- Fisher's Exact Test; [t] – Independent-samples t test

was 7.93 ± 1.47. There were 90 boys (89.1%) and 11 girls (10.9%) with a gender ratio of 9:1 (Table 1).

Of the 101 children with ASD, 49 (48.5%) had a comorbid ADHD diagnosis. Among these 49 children with ASD and comorbid ADHD (ASD+ADHD group), 15 (14.9%) had inattentive presentation, 8 (7.9%) had hyperactive-impulsive presentation, and 26 (25.7%) had combined presentation (Figure 1).

ASD clinical profile

Contrary to our expectation, there was no significant difference in all three ASD domains i.e. Social Reciprocity, Communication and Repetitive Restricted Behaviors (RRB) between ASD+ADHD group and ASD ONLY group (Table 5). All three ASD domain scores were similar between ASD+ADHD group and ASD ONLY group.

Personal and family factors

Comparing demographical data of children in the two groups by univariate analyses, we can see from (Table 2) that there were no significant gender and age differences between children with ASD+ADHD and children with ASD only. Worth noting is that the male to female ratio of 9:1 was unaltered in the ASD children regardless the presence of comorbid ADHD.

Comparing the families of the two groups of ASD children, only father's education level and mother's age at child birth were found to be statistically different while other characteristics were all insignificant (Table 3 & 4). Father's education level of ASD+ADHD group was lower than that of ASD ONLY group. Higher percentage of fathers from the ASD+ADHD group had primary or less education level (10.2% in ASD+ADHD group compared to 1.9% in ASD ONLY group) and lower percentage of fathers from the ASD+ADHD group had university or above education level (22.4% in ASD+ADHD group compared to 48.1% in ASD ONLY group) (p=0.029, Table 3). The mother's mean age at child birth in the ASD+ADHD group was younger than that in the ASD ONLY group. The mean age at child birth was 31.02 ± 4.5in ASD+ADHD group and 32.98 ± 4.32in ASD ONLY group (p=0.028, Table 4). Other clinical behaviors and difficulties and impacts.

As measured by the SDQ, the total difficulties score of ASD+ADHD group was significantly higher than that of ASD ONLY group, with ASD+ADHD group scoring 21 ± 5.28 while ASD ONLY group scored 16.98 ± 5.28 (p<0.001, Table 6). The increase in total difficulties score was contributed mostly by the increase in Externalizing Behaviors, i.e. the sum of Hyperactivity and Conduct Problem subscale scores. ASD+ADHD group scored 8.06 ± 1.65 for Hyperactivity while ASD ONLY group scored 5.85 ± 2.02 (p<0.001). For Conduct Problem, ASD+ADHD group scored 4.12 ± 2.08 while ASD ONLY group scored lower at 2.9 ± 1.35 (p=0.004). Other subscales showed no significant differences between the two groups. ASD+ADHD group scored significantly higher for Total Impact scoring 5.45 ± 2.62 compared to ASD ONLY group scoring 3.48 ± 2.64 (p<0.001). The presence of comorbid ADHD is associated with significant increase in impact in different aspects to ASD children except in Friendship (Table 7).

Multivariate analysis

Logistic regression was conducted to study the relationship between the presence of ADHD (dependent variable) and all relevant variables which were found to have significant differences (p< 0.2) in univariate analysis. Age and gender were both controlled. Thecandidate variables were put into the model with backward method and forward method was further used to double check. After conducting logistic regression analysis, only father's educational level was significantly associated with the presence of ADHD in ASD children with an adjusted odds ratio (OR) of 0.57 (95% CI 0.36-0.862, p=0.007, Table 8). In other words, ASD children with fathers who have lower education level are more likely to have ADHD.

Discussion

The present study is the first local study to report the prevalence of ADHD among Chinese children with ASD who attendeda child psychiatry clinic in Hong Kong. We found that 48.5% of children with ASD in our clinic had comorbid ADHD. While it was quoted from western prevalence studies that between 28% and 78% of ASD children had a comorbid diagnosis of ADHD [5,9,18-23], the wide range of prevalence depended on the sample source. Two community sample studies quoted a lower prevalence of ADHD: Simonoffet al. [21] reported 28.2% of their sample of ASD children had comorbid ADHD while Leyfer et al. [19] reported 31% from their sample. Whereas three clinic sample studies quoted a higher prevalence of ADHD compared to community sample: Sinziget al. 22 found that 53% of the ASD children in their clinic sample had comorbid ADHD, Ghanizadeh [9] and quoted a similar figure of 53.8% in his clinic sample, while Lee and Ousley18reported a much higher prevalence of 78% in their sample. The higher prevalence reported in clinic samples are likely due to referral bias. The reason that Lee and Ousley18 reported a much higher prevalence compared to other clinic sample studies may be due to referral bias as all their subjects were referred for a psychopharmacological consultation program at a university autism centre, which is likely to have an over-representation of ADHD. All in all, the prevalence of 48.5% of ADHD in our clinic

sample concurred with most Western clinic sample prevalence of around 53-54 %. This is significantly higher than the prevalence of ADHD among community children that is quoted 6.1% to 9% from our local epidemiological study [25].

Absence of association with ASD symptomatology

We failed to find any association between ASD presentation and the presence of comorbid ADHD in our study. As mentioned, two large scaled twin studies had demonstrated that RRB strongly correlated with all ADHD symptom domains [10,32]. The failure to establish the same association may be due to the difference in study design and target. Both twin studies assessed the subjects' ASD and ADHD symptoms from community by phone and self-reported online interview; they included children with autistic traits and ADHD symptoms that did not necessarily fulfill diagnostic criteria. This is a major difference from this study which only includes subjects from the clinic that fulfills full criteria of ASD and ADHD by structured diagnostic interviews. A possible explanation for the discrepant results is that correlation does exist between ASD and ADHD features at a subclinical trait level, but the correlation is not strong enough to persist to a disorder level; This study also has the limitations of a relatively small sample size, and that RRB could only be reflected within a narrow score range from 3 to 5 under the 3Di scoring system.

Association with parental education level

It is shown in our result that father's education level was negatively associated with the prevalence of ADHD in ASD children; i. e ASD children with fathers who have lower education level have increased rate of ADHD. This was established in both univariate and multivariate analyses. This concurred with the result of a population based cohort in Minnesota of 5,701 children which demonstrated that higher parental education levels was associated with a decreased risk of ADHD with odds ratio of 0.57-0.58 [58]. Low parental education may be a marker for parental educational difficulties due to parental symptoms of ADHD. Several studies had reported that up to 41% to 55% of families with at least one child with ADHD, at least one parent was also suffering from ADHD, suggesting a genetic component in ADHD development [59-62]. However as a preliminary study, we did not explore parental ADHD symptoms and neurodevelopmental history. Aside from genetic consideration, parental education is also frequently used as a marker of socioeconomic status, and low socioeconomic status has been associated with ADHD [63-68]. Low parental education may also be a marker for specific environmental factors affecting the risk of ADHD such as parenting style and overall family structure and functioning. Negative parenting behaviors and family disruptions had been significantly associated with ADHD symptoms [68-70].

Association with other clinical behaviors and impacts

Not surprisingly, ASD+ADHD group scored higher on the SDQ Hyperactivity subscale. However, the other Externalizing Behavior, Conduct Problem, which is known to highly comorbid with ADHD68, [71,72] was also significantly raised in this group of children. Worth noting is the lack of significant difference in other clinical domains that would have been associated with mood disorders i.e. Emotional Symptoms, or associated with ASD itself i.e. Prosocial Behaviors and Peer Problems [73]. Similarly, as could be seen in the impact subscales, the presence of comorbid ADHD was associated with significant increase in impact in different aspects (Child distress, Home impact, Classroom impact and Leisure activity) except in Friendship, a domain which is more related to ASD symptomatology itself instead of ADHD. This supports that ADHD symptoms exist distinctively in the course of ASD and echoes with the result of a lack of association of ASD symptom profile with the presence of comorbid ADHD in children with ASD.

Limitations

The findings in this study should be viewed in light of the following methodological limitations:

Clinic sample referral bias

As the sample from our study came from a tertiary care centre, the results may not apply to community samples or epidemiologically based reports. As a tertiary clinic, it is likely that the most ill children were referred for service, thus leading to inflation of apparent prevalence of comorbid ADHD among children with ASD due to referral bias.

Cross-sectional study design

The assessments in this study were all performed at a single time point. The benefit is that it allows us to compare different variables' effect with the comorbidity at the same time with little or no additional cost. However, a complete picture of comorbid ADHD presentation in ASD children may not be fully illustrated at one time point. A longitudinal approach may be of benefit for researchers to observe both disorders along the course and hence provide a more thorough understanding of the illness pattern and relationship. Nevertheless, as a preliminary study with the aim of first examining the prevalence and the associated factors' effect on the comorbidity; we believe that cross-sectional assessment is still a reliable approach.

Single informant bias

The assessments in this study rely heavily on parent as single informant. We have ascertained the diagnosis of ADHD using DISC-IV ADHD module, which has parent and youth report version. Youth version could be used for children aged 9 to 17 years while parent version is for children aged 6 to 17 years. As the mean age of my sample was 7.93 ± 1.47 years old, and youth report ADHD module was reported to have poor test-retest reliability 45 while parent version ADHD module was shown to have good test-retest reliability and validity when compared with clinician rating results [74], DISC-IV with parent as informant is believed to be a reliable source for ascertaining ADHD diagnosis.

We have not included collateral information from teachers in this study. Although multiple informants is believed to be the most reliable approach in the assessment of ADHD, there is no consensus on how to integrate multiple informant inconsistent reports systematically. Despite relying on parents to provide information regarding classroom behaviors may be less accurate, it was observed by Murray et al. [75] that parents receive more information from teachers than what teachers obtain from parents, and as parents interact with and observe their children across a wider range of settings and contexts, they may be better positioned to assess overall functioning than teachers. Therefore, despite choosing parents as the only informant has its limitation; we still believe it to be a relatively

reliable and practical means in clinical practice.

Conclusion

The present study is the first study on the prevalence of comorbid ADHD in Chinese children with ASD from a child psychiatry clinic in Hong Kong. We found that up to 48.5%, i.e. nearly one in every two ASD children who attended our clinic were suffering from comorbid ADHD. This is significantly higher than the prevalence of ADHD in local general population. The high rate together with the known detrimental impacts of ADHD comorbidity which is readily responsive to treatment raises our concern in the need to raise clinicians' alertness for early detection of comorbid ADHD in ASD children. However, upon exploration of specific clinical profiles associated with comorbid ADHD in this group of children, there was no significant difference identified in the ASD presentation which could aid early detection. This lack of clinically apparent difference in ASD children with or without ADHD makes it even more essential for clinicians to routinely screen for comorbid ADHD in every ASD children that comes to clinic.

While for the socio-demographic factors, low paternal education was found to be significantly associated with comorbid ADHD in ASD children from our study. One of the postulation of this result is parental educational difficulties due to parental symptoms of ADHD; however as a preliminary study, we did not explore parental ADHD symptoms and neurodevelopmental history.

As the first clinical prevalence study among Chinese children with ASD in Hong Kong, we have identified a high rate of ADHD comorbidity in ASD children and an association with low paternal educational level for the comorbidity. For future studies, we suggest to explore more into the neurodevelopmental background of families of ASD children with comorbid ADHD, which would be helpful towards the better understanding of the shared etiological background behind these two related yet distinct neurodevelopmental disorders.

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